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## BIOCHEMISTRY & GENETICS

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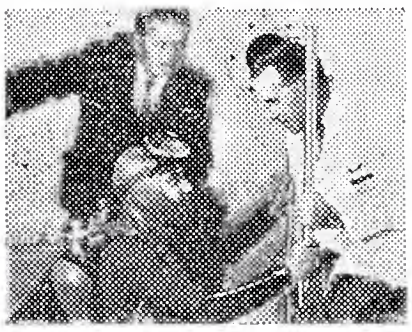

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## Guest Editorial

# *Whither Medical Research?*

Are there and will there be career opportunities in medical research? From the gradually reducing numbers of undergraduates and graduates of Medicine who are looking for training opportunities with the aim of emerging as "medical scientists", one would have to conclude that, at least in the minds of the young, the answer to this question is negative.

Is this negative answer based on facts and realities? Is there need for medical research? Therefore, should there be or should there not be career opportunities in medical research?

One should take time at this point to define terms. There are several types of medical research. Firstly, there is the enquiry into causes and mechanisms of disease with the ultimate aim of establishing methods of diagnosis, treatment and prevention. In the course of this type of research one may have to establish first the mechanisms whereby the particular function or functions operate and are controlled in the normal state.

Whenever such knowledge is inadequate or non-existent, one cannot intelligently approach the disease mechanism in question.

A second, and, in this day and age, most pertinent type of medical research is investigation into health care delivery systems, a study of methods of health care delivery applicable on a population-wide basis. The aim of this enquiry is to develop systems for the delivery of health care of a high degree of excellence, which should reach all segments of the population in an efficient and economical way.

Common to both types of medical research is the absolute necessity of rigorous application of the "scientific method". Thus, both types of research require highly-trained individuals in an appropriate scientific discipline. By necessity at least some of these required scientists must have medical training and medical experience as well. In fact, these individuals with a dual training must play a key role in medical research of any type.

Let us now turn to our questions. Is it realistic to expect that looking into the future there will be career opportunities for well-trained (and I mean rigorously trained) medical scientists? My answer to this question is yes, there must be! The argument in favor of this could best be developed by answering the second question.

# GUEST EDITORIAL

Is there need for medical research? No doubt there is a great need in our country for more practising physicians and also an appropriate number of practising specialists. But can we sit back and say that all we need to do is to apply our existing medical knowledge to problems of patients and that this will be adequate in terms of delivering health care? How many times have you students found already that many of our accepted and widely-practised methods of management are based on no facts at all? How many times have you heard or found for yourselves that there is nothing but symptomatic treatment available for the patient because, although there may be a "diagnosis", we really cannot treat intelligently since we do not know either the cause or the mechanism of the disease or both. You just have to walk through any ward of a hospital to find these unfortunate patients in significant numbers.

Looking at the problem from another point of view and taking now just our present-day medical knowledge into consideration, is this knowledge available to bear upon the health problems of every member of our society? The answer is obviously no! This is not because physicians are unwilling to look after more patients, or that they are unwilling to concern themselves with the problems of all segments of our population. There are simply not enough physicians to look after everybody, and this is particularly true outside cities, but even in large cities there are unmet health care needs. The answer is to have more medical manpower. However, can our economy support a health care system and a sufficient number of physicians to provide first-class medical services for everybody? The present health care delivery system, based mainly on services provided by a private medical practitioner, may not be within society's reach economically. The training of a sufficient number of physicians and their maintenance may be prohibitively costly. Should we then think of reorganizing health care by developing a "health team" approach employing the physician to do what he is trained for and using nurse practitioners, public health nurses, social workers, etc., who would require shorter and less costly training? Educated guesses are presently made in this area. New systems are hurriedly put together in the form of pilot projects. But what about doing some hard core research in this area? We need trustworthy epidemiological facts which are presently unavailable. We need controlled studies of effectiveness of health care delivery, but of course we do not even have the methods to measure effectiveness of health care systems. A great deal of high-powered scientific research is needed in this area as well. We should not abandon the well-proven traditional health care system before we have sound evidence to prove that a new system is better or equally good and more economical.

Based on these considerations, there must be ample scope for careers in medical research of either type. However, such careers will be available only to physicians who, besides their M.D., have had rigorous training in the scientific discipline. A great deal of money and effort can be wasted by allowing amateurs and dilettantes to mount research programmes which are badly conceived, poorly executed and thus destined to failure.

There is also a great need for scientists without medical degrees to join hands with medical researchers to work on problems that are rightly and primarily within their area of competence. In this respect there is need not only for scientists in the fields traditionally considered as basic to medicine — such as biochemistry, physiology, pharmacology, microbiology, etc., but also mathematics, physics, organic and inorganic chemistry, nutrition, psychology and others. There is a great deal of talk about overproduction of highly-trained (Ph.D. plus postdoctoral training) basic scientists. Would there be and should there be career opportunities for them in medical research? My answer is that academic clinical departments should have basic scientists on their staff to bolster their research activities. These should not be employed to be technical assistants or glorified technicians but as faculty members with equal rights and of equal standing with the clinician and the medical scientist.

The future of medical research and medicine as a whole depends to a large extent, but not exclusively, on those who make policy decisions at the highest level. Assurances must be given that support for medical research and career opportunities in medical research will be available. While a great deal must be done in order to expand research into delivery of health care, this must be kept in balance with continued expansion of research into mechanisms of disease.

However, the future of medical research, successful conduction and expansion of which is an important determinant of the future of medicine, does not only depend on decisions at the highest levels. Students and also their teachers must keep in mind that medical research may "wither" as a result of a passive and defeatist attitude on their part. Undergraduates and young graduates who have a flair for original thinking, who find themselves excited by exploration of the unknown, who find themselves making hypotheses when confronted by inexplicable events in patients, should seriously consider entering research training. Their teachers should look for them and encourage them.

*Whither* Medical Research? Will it leap forward and expand or will it "wither"?

# *Alpha$_1$ Antitrypsin Deficiency And Emphysema*

*G. Moddel,* 7T2

## INTRODUCTION

The chronic obstructive lung diseases (COLD) are by far the commonest of the pulmonary diseases. COLD is a term which applies to the diseases of chronic bronchitis, asthma and anatomic emphysema which are characterized by a persistent obstruction to bronchial airflow. The frequency of emphysema*, only one form of COLD, as a finding at autopsy is approximately 6.5%[1]. Evidently this diagnosis is not made as often during life as it should be.

Another indication of the relative importance of pulmonary emphysema is furnished by statistics on work disability allowances under the Social Security Administration in the U.S.A. In 1963, emphysema was the second most frequent primary diagnosis, arteriosclerotic heart disease being first[2].

Much work has been done in trying to find the cause or causes of this disease. Several etiological agents have been proposed: smoking, infection, air pollution, allergy, hereditary factors, aging and vascular changes. Any classification of emphysema is difficult because autopsy and clinical findings are poorly correlated. One way of classifying emphysema is by the mechanism which has caused it:

*Hypoplasia*

1) developmental bronchial anomalies
2) scar emphysema of childhood
3) bronchitis or bronchiolitis stenosans of childhood

*Atrophy*

1) aged lung
2) idiopathic centriacinar
3) idiopathic periacinar
4) coalminers pneumoconiosis
5) primary essential emphysema
6) bronchitis or bronchiolitis stenosans of adults
7) scar emphysema

*Over-inflation*

1) compensatory emphysema
2) ball-valve obstruction
3) idiopathic emphysema of childhood
4) developmental bronchial anomalies
5) bronchitis and bronchiolitis stenosans in childhood or adults
6) scar emphysema

*Destruction*

1) inflammatory
2) alveolitis as in chronic bronchitis
3) T.B.

In this article I shall discuss one possible etiology of primary essential emphysema, namely hereditary alpha$_1$ antitrypsin deficiency and I shall mention some of the interesting work being done in this centre in relation to this problem.

## ALPHA$_1$ ANTITRYPSIN DEFICIENCY

Eriksson in 1963 first discovered the relationship between an inherited biochemical abnormality and COLD[3]. He observed the almost invariable presence of severe emphysema in persons over 40 who were homozygous for an inherited plasma protein deficiency of alpha$_1$ antitrypsin. The gene was thought to be recessive, in that there was a trimodal distribution of alpha$_1$ antitrypsin activity with people with 60% of normal activity and another group with 10% normal activity. Those with 60% of normal antitrypsin activity were considered to be heterozygotes and not overtly susceptible to the development of lung disease. Eriksson estimates that the frequency of the heterozygote or carrier state was approximately 5% in the Swedish population[4].

## ALPHA$_1$ ANTITRYPSIN

It has been known for several years that human serum has the ability to inhibit the proteolytic action of trypsin. Jacobson, in 1955, demonstrated that the antitrypsin activity of human serum was confined to alpha$_1$ and alpha$_2$ globulin zones. He was able to demonstrate that about 90% of the antitryptic activity was in the alpha$_1$ globulin zone and 10% in the alpha$_2$ globulin region. In 1962 Schultze, *et al* purified the alpha$_1$ globulin trypsin inhibitor of serum and described it as an immunologically and electrophoretically homogeneous glycoprotein with molecular weight of approximately 60,000. At that time they pointed out that the alpha$_1$ inhibitor possessed antiprotease activity against both trypsin and chymotrypsin. Since then it has been shown this protein inhibits several other proteases, including elastase and collagenase.

It is possible that antitrypsin deficiency is not in itself a predisposing cause of lung disease, but that this genetic deficiency merely accommodates another closely associated chromosomal defect that is responsible. However, experiments have shown that proteolytic enzymes can induce emphysema in rodents.[5] It is currently believed that lung disease develops in antitrypsin deficient patients because their lungs are unable to withstand the action of endoproteases released from the leukocytes and

*Emphysema is an anatomic alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, non-respiratory bronchioles, accompanied by destructive changes in the alveolar walls.

macrophages in an inflammatory reaction.[4] Trypsin inhibitors have also been shown to have some antibiotic action[6] so that its absence might potentiate a lung infection.

## METHODS OF DETERMINING ALPHA$_1$ ANTITRYPSIN DEFICIENCY

The diagnosis of homozygous alpha$_1$ antitrypsin deficiency should be confirmed by measurement of the ability of the patient's serum to inhibit the proteolytic action of trypsin. Quantitative techniques have been established which colorimetrically assess the action of trypsin on a synthetic substrate. These methods measure total trypsin inhibitory capacity of serum and therefore, include the measurement of trypsin inhibition residing in the alpha$_2$-globulin fraction. The alpha$_2$-globulin trypsin inhibitor is not decreased in alpha$_1$ antitrypsin deficiency and may be increased in response to inflammation or infection[7]. In spite of this drawback the patient with homozygous alpha$_1$-antitrypsin deficiency can regularly be identified by total trypsin inhibitory capacity (TIC) values of less than 0.4 mg. of trypsin inhibition per ml. of serum. Most persons genetically proven to be heterozygous for trypsin inhibitory states will have TIC valves of between 0.4 and 0.8 mg. per ml. However, overlap with the normal range does occur.[8]

The determination of the qualitative effect of alpha$_1$-antitrypsin deficiency is done by testing the patient's pulmonary function. Some of the pulmonary function studies characteristic of severe obstructive lung disease are: a ratio of 1 second forced expiratory volume to forced expiratory vital capacity $<60\%$; a ratio of 3 second forced expiratory volume to forced expiratory vital capacity $<$ 85%; mean midexpiratory flow rate 25% of predicted; residual volume to lung capacity $>$ 60% and low gas transfer factor (diffusing capacity).

## ASSOCIATED DISEASE

With unopposed action of trypsin and other proteases it might be expected that there would be diseases of other organ systems associated with antitrypsin deficiency. A history of peptic ulcer was obtained from a higher percentage of antitrypsin deficient patients with emphysema than from patients who had normal antitrypsin activity, but the difference was small.[8] Also noted have been several cases of liver cirrhosis in infants with extremely low levels of alpha$_1$-antitrypsin, as well as an association of respiratory distress syndrome of the newborn with subnormal levels of alpha$_1$ antitrypsin.[9]

Evans, *et al* wondered if the same genetically determined deficiencies in adults which lead to emphysema, if they were present in the newborn would predispose to respiratory distress syndrome (RDS). They found decreased serum elastase inhibitor concentration in 15 of 17 newborns with the RDS and decreased serum trypsin inhibitor in 12 of 14 patients with the RDS.[10] Experimental studies on rats with induced RDS which were protected by proteolytic enzymes also implicated the action of proteolytic enzymes in preventing RDS[11].

## CLINICAL FEATURES OF PULMONARY DISEASE ASSOCIATED WITH HOMOZYGOUS ALPHA$_1$ ANTITRYPSIN DEFICIENCY

These patients present with dyspnea in the third or fourth decade. The more advanced cases on physical examination are cachectic and have shortness of breath at rest. They have all the physical signs of severe hyperinflation of the lungs, namely low fixed diaphragm, decreased or absent breath sounds with inspiratory crepitations. Neck veins are distended on expiration and the use of accessory muscle of respiration is usually prominent.

The chest x-ray shows hyperinflated radiolucent lungs, a low flat diaphragm, increased retrosternal space and decreased pulmonary vascular markings especially at the lung bases. ECG usually shows a vertical axis. Patients most severely affected show evidence of atrial hypertrophy and occasionally of right ventricular hypertrophy and strain or right bundle branch block.

## TORONTO STUDIES

A study of the relative frequency of alpha$_1$-antitrypsin deficiency was made at the Toronto General Hospital during the past year. One hundred hospital and auxiliary patients who came with any pulmonary problem were tested. The age range was from 19 to 78 years. Twenty percent were women and 80% were men. Absolute deficiency of antitrypsin was found in 5% of patients and borderline values occurred in another 5% of patients. All these patients had clinical evidence of COLD. The lowest value was found in a 42-year-old man who had had symptoms of emphysema from age thirty. As a general conclusion it was found that the lower the value of alpha$_1$-antitrypsin the earlier the onset of COLD and that a deficiency of alpha$_1$-antitrypsin was definitely associated with COLD. These figures seem to indicate that antitrypsin deficiency may be a significant cause of COLD in a selection of patients with any pulmonary disease.

## SUMMARY

It must be stressed that antitrypsin deficiency is only one factor in the complicated pathophysiological development of emphysema. Much more work has to be done before definite statements can be made but at present it does seem that the patient with alpha$_1$-antitrypsin deficiency does have a higher risk of developing COLD and also that the patient's relatives may be at risk.

If such a deficiency is found the patient should be told of the present evidence and advised to avoid pulmonary insults such as cigarette smoke, industrial air pollutants and pulmonary infections.

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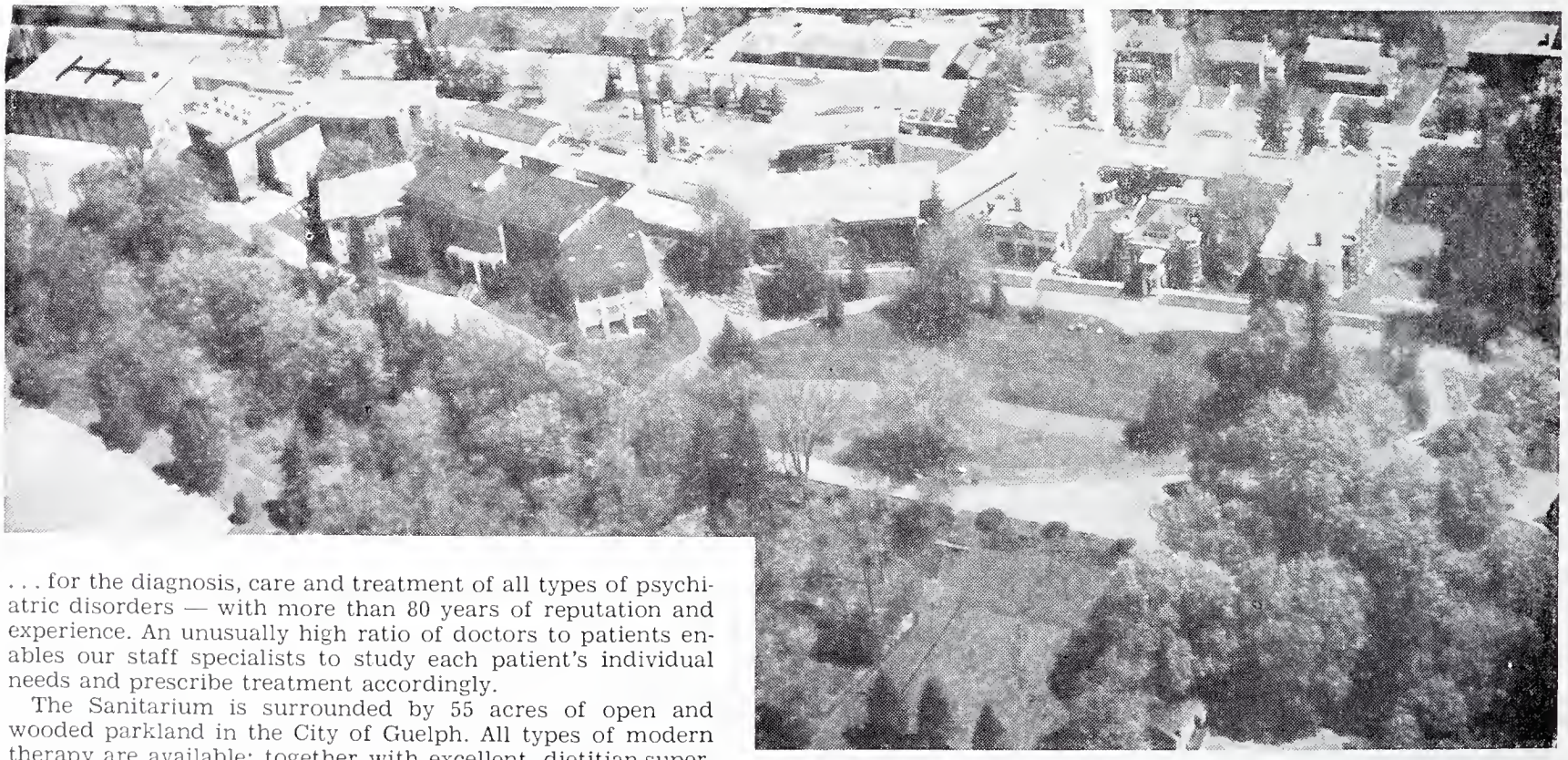

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# *Who Is Responsible?*

The explosive impact of science in the twentieth century has allowed us to see atoms and molecules, to explore the outer reaches of space and to probe Amazon jungles, Arctic plains and ocean depths. Nowhere has the impact of science been more dramatic and gratifying than in the area of medicine. Consequently, as with scientists, doctors by virtue of their expertise and great success, have been elevated to a high position in the pecking order of social status.

As a critic of the scientific hierarchy, I am struck by the parallel between practitioners of science and of medicine. Scientists and doctors receive huge subsidies from the public for the expensive business of training and practice. Yet, because of the jargon and special knowledge required for their understanding, science and medicine have remained cloaked from the prying eyes of the general public. Consequently, people in science and medicine have become a relatively autonomous elite with full powers of self-regulation and growth. Too often the vested interests of the practitioners of science and medicine conflict with those of the general public. Thus, rather than regarding themselves as public servants with the *privilege* of practicing medicine, doctors demand their *rights* of freedom to choose where, when and whom to serve and how much to earn.

Scientists have been so concerned with freedom to pursue knowledge that they often abrogate any responsibility for the application of that knowledge. Rather than assuming the responsibility of translating their work for the public to evaluate and set ethical bounds, scientists and doctors have accepted the power of making the decisions, without regard to the implications for the public. I can give you numerous examples of the failure of experts to allow public decisions on research: physicists in the Manhattan project, Del Gado's electrode implants in brains, Skinner's demands for conditioning, Edward's *in vitro* fertilization. Larson's proposal for ethnic weapons, Shockley's belief in racial differences in intelligence, Barnard's heart transplants, workers in chemical and biological warfare and the manufacturers and prescribers of drugs.

I don't mean to deny the importance of scientists and doctors in our complex technological society. But I do suggest that our unique positions are laden with special responsibilities in return for the rights to public support and trust. The recent press reports of irresponsible, bigoted statements by the President of the C.M.A., Dr. Roberts, concerning the sterilization of welfare recipients vividly demonstrate the non-concern of specialists for fact or the public. The failure of scientists to speak out on the lack of effect of LSD on chromosomes is another illustration.

Specialists must recognize the public's rights to assess all scientific and medical innovations and to make the final decisions on their implementation. The autonomy of these groups will be broken down forcibly unless enlightened members of the elites lead the way to dialogue and cooperation. Already, I fear, public demands for relevant and mission-oriented science will deal a heavy blow to basic science because scientists have failed to educate the public about science. So long as medicine perpetuates a policy of adversary we-they politics, public demands for control of the field will grow.

*David T. Suzuki*
Department of Zoology, U.B.C.

# *The Porphyrias*

*Frank W. Rosenberg,* 7T2

The porphyrias are a group of metabolic diseases characterized by the accumulation of porphyrins and porphyrin precursors of heme. Their abnormal accumulation is responsible for the clinical manifestations affecting the skin, nervous system and viscera.

*CHEMISTRY*

Porphyrins are pigments that are widely distributed throughout the animal and plant worlds as hemoglobin, chlorophyll, catalase, and as the cytochrome and peroxidase enzymes. The porphyrins consist of four pyrrole rings linked by methene bridges =CH-, whereas the porphyrinogens are colourless compounds (reduced porphyrins) with a basic structure of four pyrrole rings linked by methane-$CH_2$- bridges. Only in their reduced form are these compounds metabolically active.

*BIOSYNTHESIS*

The biosynthetic steps involved in porphyrin synthesis are as follows. Acetate enters the Kreb's cycle and is converted to succinyl CoA, in the presence of ATP and magnesium ions. The enzyme delta amine levulinic acid synthetase (ALA-synthetase) with pyridoxal phosphate as coenzyme catalyses the condensation of glycine and succinyl-CoA to form $\alpha$-amino $\beta$-ketoadipic acid which spontaneously breaks down to delta amino levulinic acid (ALA). These events are localized in the mitochondria.

Two molecules of ALA in the presence of glutathione (GSH) and the enzyme ALA-dehydrase condense to form a monopyrrole porphobilinogen (PBG), which contains an acetic acid and a propionic acid side chain. Four molecules of PBG condense to form two natural isomers (I or III) of the tetrapyrrolic compound uroporphyrinogen (UPG). Normally UPG III makes up 99% and UPG I 1%. UPG III, the isomer essential for heme production is formed by the combined action of two enzymes PBG-deaminase and UPG-isomerase. A deficiency or absence of UPG-isomerase results in the production of a type I UPG which cannot be used for heme synthesis. Type I porphyrins are waste products.

Uroporphyrinogen III is converted to coproporphyrinogen III (CPG III) by the enzyme UPG-decarboxylase. CPG III is then converted to protoporphyrinogen IX in the presence of the enzymes CPG-oxidase and CPG-decarboxylase. CPG-oxidase acts specifically on type III CPG. Protoporphyrinogen IX undergoes autooxidation to protoporphyrin IX, which is converted to hemoglobin in the presence of the ferrous ion ($Fe^{2+}$), GSH, globin and the enzyme ferro-chetalase. The chemistry and biosynthetic steps leading to the formation of hemoglobin can be found in any standard text of Biochemistry.

It is noted again that only the type III porphyrins are involved in heme synthesis. Type I porphyrins cannot be used and are excreted as waste products whether production is normal or abnormal.

*EXCRETION*

Normally ALA and PBG are excreted in the urine in only minute amounts. Protoporphyrin IX is present in small amounts in urine and feces. Coproporphyrin is the predominant porphyrin excreted in the urine and feces of most normal individuals. Only trace amounts of uroporphyrin are normally excreted in the urine.

In the *porphyrinurias,* there is an increased excretion of porphyrins in the urine and feces, which is not related to any abnormality of porphyrin biosynthesis, but which is secondary to hemolytic anemias, liver disease, polio, and lead poisoning. The colicky pain and neuropathy of lead poisoning can simulate that seen in acute intermittent porphyria (AIP). High urinary excretion of coproporphyrin is often characteristic of lead poisoning. However, excessive urinary excretion of PGB, characteristic of acute intermittent porphyrins is never a feature of lead poisoning.

*CLASSISFICATION*

The porphyrias may be divided into two general groups. In the erythropoietic porphyrias, there is excess porphyrin accumulation within normoblasts and erythrocytes. In the hepatic porphyrias, excess porphyrin or porphyrin precursor production occurs in the liver. The following is a more detailed classification:

Table I

I. Erythropoietic Porphyrias
   - A. congenital erythropoietic porphyria
   - B. erythropoietic protoporphyria

II. Hepatic Porphyrias
   - A. genetic:
     1. acute intermittent porphyria (AIP)
     2. porphyria variegata
     3. porphyria cutanea tarda
     4. hereditary coproporphyria
   - B. acquired:
     1. alcoholism
     2. toxic (hexachlorobenzene induced)
     3. secondary to hepatoma
   - C. experimental (Sedormid given to rats)

*CLINICAL DESCRIPTION OF TYPES*

I. Erythropoietic Porphyrias

A. In *Congenital Erythropoietic Porphyria,* excessive uroporphyrin I is found in the marrow, in circulating erythrocytes, in the plasma, urine (which consequently is red in colour), and feces. Lesser amounts of coproporphyrin I are also found in the excreta, but excretion

of all other porphyrins is normal. Uroporphyrin I accumulation at the expense of the needed type III results in a hemolytic anemia from birth onwards, which is often accompanied by splenomegaly. In other words too little uroporphyrin III as a result of deficient UPG isomerase, gives rise to too little heme and thence a clinical anemia. The patient excretes a burgundy-red urine or a urine that turns red upon exposure to light. Splenectomy often improves the hemolytic anemia and also reduces porphyrin excretion. The teeth of affected individuals are pinkish, as a result of porphyrin infiltration.

The uroporphyrin I accumulation is also responsible for a severe photodermatitis. Photodynamic blisters occur on the exposed surfaces, especially of the face and hands. Skin not exposed to light remains unaffected. In time, scarring and extensive mutilation, such as loss of fingers and portions of ears, contribute to morbidity. There is no significant disturbance of the nervous system, nor is there any abdominal colic. The disease is progressive, and death is usually due to an intercurrent infection or to severe hemolytic anemia. Quinine cream and avoiding sun exposure ameliorate the associated dermatosis. The condition is inherited as a Mendelian recessive.

B. *Erythropoietic protoporphyria* is the commonest erythropoietic porphyria. It is transmitted as an autosomal dominant characteristic. Biochemically, there is an increase in the protoporphyrin content of normoblasts, erythrocytes, plasma and feces. The urinary excretion of porphyrins is normal, and hence the urine is normal in colour. Erythropoietic protoporphyria is essentially a dermatosis precipitated by sun exposure. Two main types of skin lesions are characteristic:

1) a banal urticaria without sequelae
2) erythema, edema and an ensuing eczematous eruption on the exposed parts that leaves considerable scarring

Avoidance of excess sunlight is often satisfactory treatment. Application of sun-screening creams protects the skin from near ultra-violet rays (380-420 A).

## II. Hepatic Porphyrias

Most of the hepatic porphyrias are transmitted as autosomal dominants. Visceral, neurologic and dermal manifestations can occur singly or together.

### A. Genetic types

1. *Acute intermittent porphyrias* (*AIP*) affects young or middle aged adults especially females. The disease is characterized by:

1) periodic attacks of intense abdominal colic accompanied by nausea and vomiting;
2) obstinate constipation;
3) neurotic or even psychotic behaviour;
4) neuromuscular disturbances.

Biochemically, there is excessive excretion of porphobilinogen (PBG), uroporphyrin I and III, coproporphyrin I and III, amino-levulinic acid (ALA) and other, as yet unidentified, porphyrins. Marrow aspiration reveals a normal porphyrin content, but excessive porphyrins and porphyrin precursors are found in the liver. During an acute attack of AIP, ALA-synthetase activity is increased seven-fold. Between acute attacks or in the latent asymptomatic phase, the ALA-synthetase activity is still above normal. An acute attack more commonly occurs without any truly obvious external precipitant. Less commonly, barbiturates, estrogens, 5-beta-hydroxy steroid metabolites, etc., can induce or raise the already high or "latent" ALA-synthetase activity to that characteristic of the acute attack.

#### *MOLECULAR BIOLOGY OF AIP*

A structural gene (part of a chromosome) bearing the template for the protein to be synthesized transcribes a replica of itself in messenger RNA, which migrates to polyribosomes in the cell where it is "translated" into polypeptide chains. Transcription of the structural gene to mRNA is always initiated at the same site on the gene, designated the "operator" whose functional unit is called the "operon". It is also assumed that a regulator gene exists at some distant genetic locus and that this gene synthesizes a "repressor substance" capable of binding the operator site, so that operon activity is minimized.

To account for the increased "basal" ALA-synthetase activity seen in the latent or asymptomatic phase, the operon must somehow be *derepressed* so that transcription and enzyme synthesis can proceed unchecked. *Derepression* at the operon site can be accomplished by any of the following means:

1) production of too little repressor;
2) production of defective repressor;
3) defect at the operon binding site.

Postulate 3) seems the most acceptable, since, as will be illustrated in the following section on genetics, such a mechanism is consistent with the autosomal dominant pattern of inheritance of AIP.

In the above, an explanation was given for the "basal" increase in ALA-synthetase activity seen in the latent or asymptomatic phase of AIP. The mechanism of enzyme inductibility now follows. ALA-synthetase catalyzes the rate limiting step of heme synthesis, and heme exerts a simple negative feed-back inhibition on this enzyme system. Granick[1] has postulated that the repressor protein formed by the regulator gene is composed of an apoprotein plus heme (end product of the pathway); that is, repressor equals apoprotein plus heme. Barbiturates are thought to compete with heme for apoprotein binding. The new repressor, namely apoprotein plus a metabolite of barbituric acid is however a defective repressor. Hence, whenever a barbiturate is taken, the operon site is *derepressed* and ALA-synthetase synthesis is allowed to proceed unhindered, resulting in an in-

creased urinary PBG and in an attack of AIP. Heme, therefore, exerts this *feedback repression* as well as the aforementioned negative feedback inhibition on heme synthesis in general and on ALA-synthetase in particular.

An explanation must still be found for the sudden acute attacks that are not preceded by any obvious external precipitants. At these times, there simply may be an occult stress on the hematopoietic system, whereby more heme is required. A relative depletion of heme working via feedback inhibition and feedback repression could "induce" the production of ALA-synthetase and hence could precipitate an acute attack.

*GENETICS OF AIP*

Perlroth, *et al*[2] and Granick[3] have tried to explain the autosomal dominant inheritance of AIP and the increased basal activity of ALA-synthetase in terms of a lesion at the operator site. If there were a mutation on one allele of the *regulator* gene, the other normal regulator gene would still be producing repressor effective on both of the distant operons responsive to it. Such a cell would therefore be indistinguishable from the normal condition where both alleles produce repressor. In order for a regulator gene mutant to be phenotypically recognizable in a diploid cell it would have to be homozygous (Mendelian recessive). AIP, however, is known to have a dominant pattern of inheritance (i.e. manifest in succeeding generations).

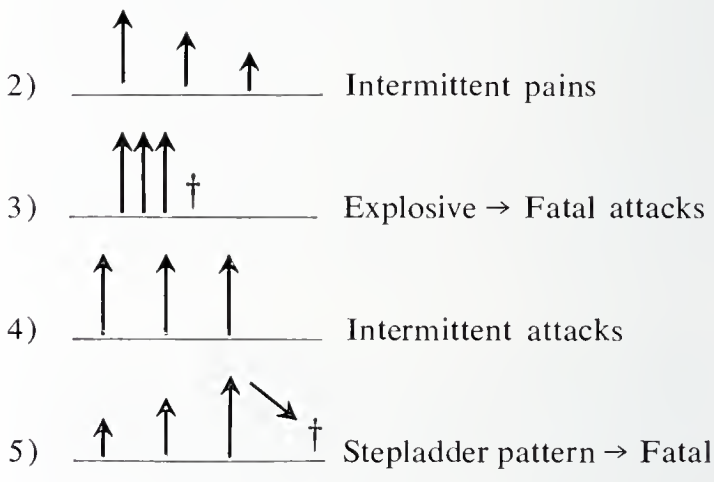
Alternatively, a mutation of an operator site (postulate 3 above) so that repressor substance could no longer inhibit transcription, would maintain enzyme production at a high level. Such an organism would be using one allele unresponsive to repressor substance for constant unregulated "basal" enzyme production in the latent or asymptomatic phase, consistent with an autosomal dominant pattern of inheritance. Furthermore, as mentioned in the above, the competing of inducing drugs with heme for the repressor apoprotein accounts for the sudden increase in ALA-synthetase activity (*inductibility*).

*CLINICAL FEATURES OF AIP*

The course of AIP is variable (see Fig. 1). Recurrent abdominal crises may be present for years, or the patient may die in the first attack. Severe colicky abdominal pain accompanied by vomiting and constipation is often the presenting complaint. The pain is usually confined to the epigastrium or to the right iliac fossa. There is very little muscular rigidity or tenderness. Because of the accompanying fever, tachycardia and leucocytosis, the abdominal symptoms are frequently mistaken for those of acute pancreatitis, acute cholelithiasis, renal colic or acute appendicitis. Stein and Tchudy[4] report that an autonomic neuropathy induces the abdominal symptomatology and often also induces tachycardia and postural hypotension. Transient hypertension, however, may accompany an attack. Darkening of the exposed skin can occur in AIP; nevertheless, there is usually no photodermatitis.

The neurologic manifestations may simulate poliomyelitis, encephalitis, arsenic or lead poisoning. Often a patchy demyelination is responsible for a peripheral neuropathy with hypoesthesia, paresthesiae in the lower limbs, foot and wrist drop, and a decrease in proprioceptive and vibration sense. Spotty weakness or paralysis, especially of the wrist and finger extensors with diminished or absent tendon reflexes can supervene. Involved muscle groups are often tender.

Figure 1




Cranial nerve involvement is possible with diplopia, dysphagia, dysarthria, aphonia, or facial palsy and, in severe cases, lethal bulbar encephalopathy with respiratory paralysis. Generalized or focal epilepsy can supervene, and barbiturates must not be used in its management.

Possible psychiatric accompaniments range from depression to acute psychosis. Many patients during an acute attack are confused and anxious, often obsessed by delusions, hallucinations or suicidal thoughts. Patients complain of insomnia and can exhibit ambivalence and depersonalization along with an immature personality.

It is evident that clinically, AIP resembles hyperthyroidism with a sinus tachycardia, emotional lability and muscle weakness. Biochemically there is an increase in total T-4, yet there is a normal level of circulating free T-4. An increase in thyroid binding globulin, in thyroid binding capacity and in PBI are also characteristic. Per cent uptake of radioactive iodine is normal. Hence, there is really only a "pseudohyperthyroidism", similar to that seen in pregnancy or in patients on oral contraceptives.

The ESR is normal during an attack. The BUN and serum creatinine can be raised. There is usually a slight leucocytosis. CSF examination is normal even in an acute porphyric neuropathy or encephalopathy. A mild transient hypertension can occur. Hepatic dysfunction is not a feature of an acute attack.

The polyneuropathy of AIP affects motor fibres (esp. of proximal muscle groups) more than sensory fibres, and long fibres more than short ones. There is still considerable controversy as to whether the lesions are due to a toxic demyelination by high porphyrin levels (a theory that is being gradually discarded) or to a trophic degeneration secondary to a relative deficiency of vitamin $B_6$.

Pathologically, the nerve lesions closely resemble those seen in isoniazid induced pyridoxine deficiency. It is postulated that since pyridoxine is a cofactor for the enzyme ALA-synthetase (which is increased in AIP), body stores of pyridoxine are depleted. Supplementation of pyridoxine, however, gives no improvement. Active regeneration is usually the rule in porphyric neuropathy.

Elder and Mengel[5] postulate that the ALA-synthetase in AIP may be an *altered form* of the enzyme, that avidly uses up most of the tissue pyridoxal phosphate. They provide evidence for this postulate by an indirect measurement of pyridoxine during an acute attack of AIP.

The metabolic degradation of L-tryptophan requires pyridoxine. If pyridoxine is lacking the metabolism of L-tryptophan is redirected so that increased levels of xanthenuric and kynurenic acids appear in the urine. Elder and Mengel found increased titers of xanthenuric and kynurenic acids in the urine of patients during an acute attack of AIP when loaded with L-tryptophan. Therefore, the more pyridoxine given during an acute attack of AIP, the more will be avidly consumed by the "*altered*" ALA-synthetase during an acute attack. In other words, pyridoxine supplementation is of no therapeutic benefit. In fact many workers advise pyridoxine restriction during an acute attack, so as to deprive the overactive enzyme of its co-factor.

Many authors attribute the tachycardia of an attack of AIP to an autonomic cardio-neuropathy of the vagus nerve or of its brain stem nucleus. The lesion, most probably an acute demyelination is quickly reversible. A comparable tachycardia is seen in a severe Guillain-Barré syndrome or post-infectious polyneuropathy, where the demyelination is of an "auto-immune" origin. The cardio-neuropathy of AIP is probably metabolic (pyridoxine deficiency) or toxic (excess ALA and PBG). The acute and reversible hypertension seen in an acute attack of AIP can be attributed to an interruption of the sino-aortic reflex by the acute neuropathy of the afferent loop.

Neuroendocrine dysfunction is manifest by the inappropriate release of growth hormone, failure to secrete ACTH (isolated deficiency without the involvement of other trophic hormones) and most signficantly the syndrome of inappropriate ADH secretion. Perlroth, *et al*[2] found a specific hypothalamic lesion at the autopsy of a patient with AIP. The median eminence showed a chronic cell infiltrate with reactive astrocytes; the supra-optic and para-ventricular nuclei showed neuronal loss, and glial cells. Drawing upon this finding, many subsequent authors relate the characteristic neuroendocrine dysfunction to such lesions.

Hyponatremia is common during the acute attack. The serum is hypo-osmolar and the urine hyper-osmolar. Sodium, however, could be lost in the course of the vomiting and diarrhea of an acute attack. Possible renal tubular defects in the handling of sodium must also be considered. Thus, when a patient with AIP is water repleted, release of ADH results in water reabsorption by the kidney and can eventually bring about water intoxication. The sequelae of water intoxication (serum Na of 100 meq./1) include stupor and convulsions, both of which can characterize an acute attack.

Simple water restriction or injection of hypertonic saline will usually bring about a remission of symptoms. In summary, an attack of AIP is characterized by a hyponatremia-hypochloremia and by a natriuresis. Extensive urinary loss of calcium can occur with an eventual tetany.

Stein and Tschudy[4] found that one-half of the patients in their study failed to respond to a glucose load with the suppression of growth hormone release. In their study most symptomatic patients with AIP also had abnormal glucose tolerance curves. Insulin secretion measured in these patients was delayed and excessive in a similar fashion to that seen in "pre-diabetes mellitus". In other words, the glucose tolerance curve has early elevated blood sugars, and a late reactive hypoglycemia. Nevertheless, a glucose load in AIP yields high levels of pyruvate and lactate; whereas a glucose load in diabetes mellitus yields low levels of pyruvate and lactate. Normally, the carbohydrate introduced into a cell by insulin, either, undergoes glycolysis to pyruvate and lactate, or, undergoes synthesis to triglyceride. In an acute attack of AIP, however, the carbohydrate is preferentially metabolized to lactate and pyruvate. Many workers, therefore describe a defect in the intracellular utilization of carbohydrate in AIP. Surprisingly, exogenous insulin reverses the abnormalities of glucose, lactate and pyruvate metabolism after a glucose load.

Between acute attacks the glucose tolerance curve is normal. Interestingly, in Stein and Tschudy's study[4] the inappropriate growth hormone release was not the fundamental mechanism of the carbohydrate intolerance, since the two phenomena occurred indcpendently.

Many studies have shown that the output of porphyrin precursors varied inversely with the amount of carbohydrate and/or protein ingested. This "glucose effect" is probably due to the inhibition of the induction of ALA-synthetase by high carbohydrate levels. Shemin[6] has postulated that this carbohydrate inhibition mechanism is based on the concept of two competing intracellular reactions, i.e.

Ac-CoA + Glycine → aminoacetone (1) step in amino acid metabolism
Succ-CoA + Glycine → ALA (2) ALA synthesis

If the cell obtains more carbohydrate or its eventual metabolite Ac-CoA, reaction (1) is preferred over reaction (2) and less ALA is synthesized. Recently, however, Tschudy[4] has found normal amounts of aminoacetone during an acute attack.

Nevertheless, a high carbohydrate diet works well therapeutically, especially in conjunction with exogenous insulin. Barbiturates and estrogens must be avoided. During acute attacks morphine or meperidine provide satisfactory analgesia. Chloral hydrate is good for sedation. Chlorpromazine in doses of 50 to 100 mg. rapidly relieves acute symptoms. Water restriction may become necessary during the acute phase of the inappropriate secretion of ADH.

Next to syphilis, porphyria is the "great imitator". An acute attack can mimic any acute abdomen. The diagnosis is even further precluded by a co-existing peptic ulcer disease or by a superimposed acute pancreatitis. The diagnostic triad of unexplained abdominal pains, unexplained peripheral neuropathy and unexplained psychosis should alert the clinician to test the urine for porphobilinogen.

As useful prophylaxis all family members and close relatives should be checked out for asymptomatic porphobilinogenuria. Family members can have the gene with an expression so reduced that they may not excrete excess PBG in the urine. No family members should therefore be given barbiturates. Pregnancy and the puerperium can be precarious times for a porphyric.

2. In *porphyria variegata* skin lesions are common in males, whereas acute visceral attacks are more frequent in females. Porphyria variegata is clearly transmitted as an autosomal dominant wherein 50% of the adult members of affected families show constant increased excretion of coproporphyrin and protoporphyrin (see Table II) in the feces whether symptoms are present or not.

Photosensitivity is characterized by blisters, abrasions, and hyperpigmentation. Acute attacks of abdominal colic and acute psychosis intervene, wherein porphyrin excretion in the feces often decreases with a corresponding increase in urinary porphyrins (ALA, PBG, coproporphyrin, uroporphyrin). Excretory levels of ALA and PBG are normal during a remission. Sunlight and drugs (barbiturates, estrogens, choloroquine, griseofulvin, ethanol, iron compounds, phenylhydrazine) should be avoided.

3. *Porphyria cutanea tarda* is an acquired dermatosis in which abdominal pain and neurologic manifestations are absent. Biochemically, large amounts of uroporphyrin but normal amounts of ALA and PBG are excreted in the urine and feces. Alcoholism and hepatic dysfunction are common accompaniments. In 40 to 50 year old males, after sun exposure or minor trauma, the affected area of skin becomes red and vesicles and bullae appear. Hyperpigmentation and a tendency to easy abrasion are also present. Commonly the face, neck, and backs of the hands are affected with the subsequent development of areas of pigmented atropic and scarred skin. Hypergammaglobulinemia, abnormal BSP excretion, high levels of SGOT and abnormal exocrine and endocrine pancreatic function are features of this "acquired hepatic porphyria". Iron metabolism can be deranged with iron overloading, high serum iron and iron saturation, and polycythemia. Diabetes mellitus is present in almost one quarter of these patients. Infrequently, porphyria cutanea tarda can be found in association with internal malignancies. It has been proposed that there are abnormalities in the oxidation - reduction enzyme systems in the liver, whereby intermediate porphyrinogens on the pathway to protoporphyrin are oxidized to their corresponding porphyrins which, when irradiated derange the cellular lysosomes in the skin. Characteristic vesicular and bullous lesions result.

Alcohol and precipitating drugs (barbiturates, chloroquine, griseofulvin, iron compounds, estrogens and phenylhydrazines) must be avoided. Phlebotomy is the best method of managing patients with increased serum iron levels. A good, prolonged remission with the disappearance of all clinical signs of skin fragility and photosensitivity can often be anticipated.

4. Only 30 cases of *hereditary coproporphyria* have been described. The condition is inherited as a Mendelian dominant. Its unique feature is an increased excretion of coproporphyrin III during the latent asymptomatic phase and during the active phase of acute abdominal attacks. Urinary levels of ALA and PBG are also increased during acute attacks. Barbiturates, certain tranquilizers and anticonvulsants provoke attacks. Psychiatric symptoms are commonly present.

B. *The acquired porphyrias* (see Table I) have identical features to those of porphyria cutanea tarda which, although constitutionally determined is precipitated by long-standing alcoholic liver damage. Designation of a case as purely acquired depends on the failure to demonstrate latent or manifest porphyria in the patients' relatives.

1. *Acquired porphyria* is found as a rare complication of hepatic cirrhosis that is secondary to alcoholism or to malnutrition. It can also occur as a complication of hepatoma, Hodgkin's disease, leukemia, or systemic lupus erythematosus. Red urine due to the presence of uroporphyrin is the clue that usually leads to the diagnosis.

2. Five thousand cases of acquired porphyria in Turkey have been traced to the dietary consumption of seed wheat that had been treated with a fungicide, *hexachlorobenzene*. The resultant syndromes, seen mostly in children featured cachexia, hepatomegaly, bullous skin lesions, photosensitivity, hyperpigmentation, hypertrichosis, and increased porphyrin content of ex-

Table II

| Features: | ERYTHROPOIETIC | | | HEPATIC | | | |
|---|---|---|---|---|---|---|---|
| | Cong. | Proto porphyria | Copro porphyria | A.I.P. | Porphyria variegata | Cutanea tarda | Hereditary copro-porphyria |
| Inheritance | recess. | dominant | dominant | dominant | dominant | acquired | dominant |
| Sex | both | both | | both | both | both | both |
| Age of Onset | 0-5 | 0-5 | ..... | 15-40 | 10-30 | any age | any age |
| Photosensitivity | + + + | + | + | — | ± | + + | ± |
| Abdominal and/or neuro-psychiatric | — | — | — | + + | ± | — | ± |
| RBC | | | | | | | |
| uroporphyrin | + + + | + | + | } normal | } normal | } normal | } normal |
| coproporphyrin | + + | + | + + + | | | | |
| protoporphyrin | + | + + + | + | | | | |
| Urine | | | | | | | |
| colour | red | normal | normal | red or black on standing | red or black on standing | red | normal |
| ALA | normal | normal | normal | + + | + + (acute) | normal | + |
| PBG | normal | normal | normal | + + + | + + (acute) | normal | + |
| uro + coproporphyrin | + + + | normal | normal | + + | + + (acute) | + + + | + |
| Feces | | | | | | | |
| Copro + urotoporphyrin | + + | normal | normal | + | + + + + | + + | + + |

creta. A chronic porphyric state was induced, for all porphyric features persisted in most patients for at least two years after the cessation of hexachlorobenzene ingestion. Even five years later, most patients were still symptomatic with the added feature of a delayed onset rheumatoid arthritis.

*LABORATORY ASSESSMENT*

Measurement of a) urinary ALA, urinary PBG, b) fecal porphyrins, c) miscellaneous urinary porphyrins, and d) free erythrocyte porphyrins constitutes a complete biochemical investigation of a suspected case of porphyria. All of the patient's near relatives should also be investigated.

Measurement of a) urinary porphobilinogen is an adequate screening test. A red coloured complex forms upon the addition of Erlich's reagent (2% w/v p-dimethylaminobenzaldehyde) in 5 *N* HC1. The reaction is strongly positive in AIP, porphyria variegata, and hereditary coproporphyria. False positives can occur with urobilinogenuria and with the widely used urinary analgesic pyridium.

The *urine* colour is a poor indicator of the actual concentration of *porphyrins*. Due to the excess PBG, the urine in an acute attack of AIP or porphyria variegata turns from a normal colour to a deep-red and eventually to a brown or even black simply upon standing. The process is speeded by heating and/or by the addition of acid. Porphobilinogen, however is colourless in the urine, whereas uroporphyrin which is not excreted in the urine is red. The following reaction therefore occurs non-enzymatically:

$$\text{PBG} \xrightarrow[\text{heat}]{\text{UV}} \underset{\text{"red"}}{\text{uroporphyrin}} + \text{non-porphyrin pigment (dark brown or reddish)}$$

The urine in porphyrin variegata can be normal in colour. As mentioned in the above, the urine in congenital erythropoietic porphyria is red, whereas the urine in erythropoietic protoporphyrin is normal in colour. When urinary porphyrins are extracted into organic solvents, such as amyl alcohol, they fluoresce red under ultra-violet light in a dark room.

A positive reaction for urinary porphyrins is also seen in the porphyrinurias, e.g. poliomyelitis, rheumatic fever, anemia, alcoholic cirrhosis and carbon tetrachloride poisoning.

*Fecal porphyrins* are extracted with amyl alcohol and fluoresce under ultra-violet light in direct proportion to the actual concentration of porphyrins. Fecal porphyrin extraction in pre-pubertal latent porphyrics is usually negative, whereas the urinary extraction usually yields a positive result. (A latent porphyric is often an asymptomatic relative of a symptomatic patient who excretes above normal levels of ALA, PBG or other prophyrins.)

The determination of an increase in *erythrocyte protoporphyrins* for a diagnosis of an erythropoietic porphyria is made by mixing: whole blood + ether + glacial acetic acid + HCL, which will fluoresce red under ultra-violet light.

Porphyria has historical as well as biochemical, genetic and clinical significance. King George III of England

suffered from classic AIP as deduced from recently discovered records. He had bouts of:

1) colic and constipation;
2) painful paresis of arms and legs;
3) vocal paresis;
4) tachycardia and sweating attacks (autonomic lesions);
5) insomnia, delirium, stupor, fits (encephalopathy);
6) dark urine on standing.

The success of the American Revolution has often been attributed to George III's ineffective political and military firmness, during his "unexplained fits". "So long as it was believed that he (George III) suffered from insanity every aspect of his life and character was seen in a distorting mirror".

AIP, through its Mendelian dominant inheritance was spread by constant intermarriage throughout the royal houses of Stuart, Hanover and Prussia. Mary, Queen of Scots (1542-1587) began this "royal porphyric tradition."

The prophyrias are of interest to both clinicians and biochemists. The diagnostic and physiological aspects of these diseases encompass many areas of internal medicine, neurology, dermatology and psychiatry. Much has yet to be learned of the exact pathophysiology of the conditions.

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# *SHOUT: Interdisciplinary Education In Community Health Care*

*Paul Finnegan, 7T3*

The Student Health Organization of the University of Toronto (SHOUT) was founded in 1967 by a small group of health science students who felt their undergraduate education to be somewhat inadequate. They felt that the traditional health science curriculum provided no opportunity for students from different health science faculties to interact with one another and that curriculum constraints did not allow students to participate meaningfully in providing care for the community which they were being trained to serve. The fact that their undergraduate education effectively separated them from each other and from community service prompted the students to attempt the independent development of an alternative in undergraduate health science education which did, in fact, bring the students together and did allow them to make a valuable contribution to the community.

## HISTORY AND DEVELOPMENT

The SHOUT program began in the fall of 1967 as students organized a number of informal seminars to discuss problems related to the social and psychological aspects of health and health care delivery. The health and social problems of the Indians and Eskimos were considered at several of these seminars as were the problems of the urban poor. Special emphasis was placed on the problems encountered by this latter group in attending hospital out-patient and emergency clinics where long waits were commonplace and inconvenient and where the staff often seemed impersonal and uncaring.

As well as participating in seminar groups, SHOUT members were active as volunteers in a number of community organizations. A few students worked in teen drop-in centers; some worked with children's agencies as tutors and as recreation supervisors; and still others were involved in a program of familiarizing recent immigrants with the city and its resources and helping them to settle in their new surroundings.

The SHOUT program of informal seminars and volunteer participation in community social service agencies continued until the fall of 1968. By this time the students had come to realize that what they really wanted was an opportunity to work together in the provision of primary health care for the low income groups whom they felt to be somewhat disenfranchised within the traditional health care system. SHOUT decided, then, to open a 'storefront health clinic' where people could walk in off the street and receive prompt and personal attention to their medical and social needs. The clinic was to be modelled along the lines of the community health centers which had recently been developing in the United States.

In 1964 the United States Office of Economic Opportunity had begun to act in the field of health by making funds available to plug specific loopholes in existing publicly supported services. Several practical demonstrations indicated that the basic arrangements — government and private — whereby health services were made available to the underprivileged were defective; and that to the extent that health services were relevant to health status, the health of the underprivileged would not be improved without fundamental changes in the arrangements whereby health services were organized and delivered. Out of this came the concept of the 'Community Health Center' — the basic characteristics of which were envisaged as follows:

1. Focus on the health needs of the underprivileged.
2. A one-door facility readily accessible in terms of time and place in which virtually all ambulatory health services are made available.
3. Assurance of personalized, continuous, high quality care.
4. Full integration with existing sources of health services.
5. Close coordination with other community resources.
6. Intensive participation by the population to be served, both in policy making and in employment.
7. Sponsorship by a wide variety of public and private agencies.

After talking with several local health and social service professionals and canvassing a number of low income neighbourhoods within the city core, SHOUT decided to locate its 'storefront health clinic' in Alexandra Park. In February 1969 the original SHOUT clinic opened in rather cramped quarters above a shop on Bathurst Street, the western border of Alexandra Park. The clinic was open for medical patients four nights each week and was staffed by student volunteers working under the supervision of licensed physicians. Patients were few and far between but neighbourhood children flocked to the clinic in droves in understandable attempts to relieve the tedium of their inner-city lives. SHOUT responded to these children by developing a 'Kids' Program'; movies were shown, square-dancing was taught, sports activities were supervised and tours of the city were organized. However, the health care program never really got off the ground. In fact, some students thought that the children were scaring the patients away.

Later in 1969 SHOUT decided to move more centrally into its service area and in November the Alexandra Park Community and Health Center opened in an eight-room, semi-detached house at 64 Augusta Avenue — dead square in the middle of Alexandra Park. (Figure 1).

For the first six months the new Center was open four nights each week, Monday through Thursday, as medical and nursing students worked under professional super-

FIGURE I A Map of Alexandra Park

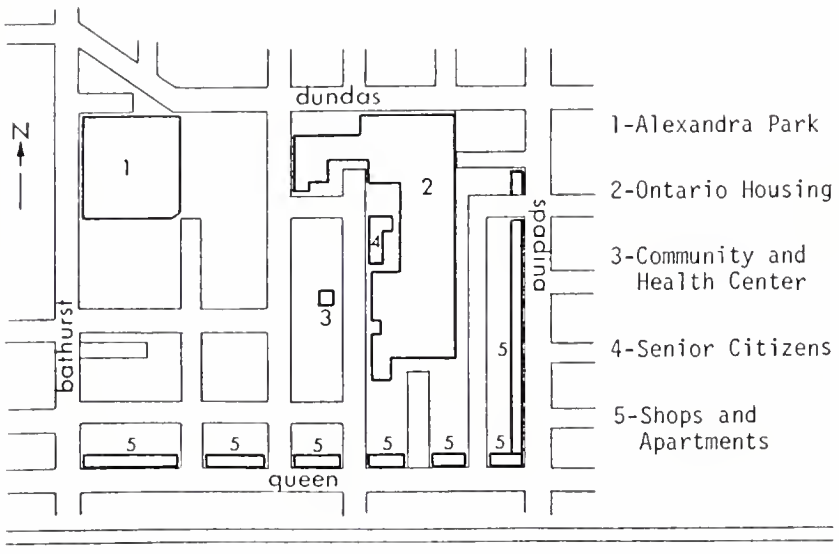


FIGURE 1

Alexandra Park is defined as being that community within the city block bounded by Dundas, Spadina, Queen and Bathurst. The community takes its name from a large park which is located in its northwestern corner. It is possible to identify three subcommunities within the block on a simple geographical basis. The first of these is represented by the Senior Citizens building which houses some 311 pensioners. It is located at 91 Augusta Avenue. The second subcommunity is the Ontario Housing Corporation Alexandra Park Housing Development. This development has 410 housing units for low income families. Finally, there is what we refer to as Alexandra Park West, an area consisting of privately owned residential housing. Included in Alexandra Park West are a number of apartments which are above the shops and restaurants located along the Spadina and Queen borders of the block.[6]

vision to provide basic medical services for the trickle of community residents who presented themselves at the clinic. In April of 1970 the long awaited dental clinic opened and senior dental students, with the aid of faculty supervisors, manned three secondhand dental chairs and attempted to meet the seemingly inexhaustible demand for the free dental services which they were providing. In October of the same year private and government funding allowed SHOUT to hire a secretary and a public health nurse and to purchase badly needed supplies and equipment. In January 1971 two physicians were hired to provide medical consultations on six halfdays per week — in addition to the continuing evening program. A 'doctor-on-call' system was established at that time to ensure that a physician be available to the community at night and on weekends. The patient load at the Center and the number of students participating in the SHOUT program increased so dramatically in the first eighteen months of the Center's operation that SHOUT decided to exercise its option to lease the adjoining premises at 62 Augusta and to expand its facilities. Construction was begun in March 1971 that in a few months turned the Alexandra Park Community and Health Center into a fully equipped medical-dental clinic with additional space for educational and community activities.

## THE EVENING VOLUNTEER PROGRAM

At the present time the core of the SHOUT operation is the evening volunteer program. Students from the faculties of Dentistry, Medicine, Nursing, Pharmacy and Social Work have joined together in a series of 'interdisciplinary health teams' to provide primary health care for the residents of Alexandra Park, and to learn professional and personal skills in the process. Each of the eight evening teams works at the Center on a regular rotation, once every two weeks, while three additional teams run a 'mother and child clinic' on Saturday mornings.

A typical night at the Center begins around 6:30 as the students and their supervisors hold a 'pre-clinic meeting' to plan the evening's activities. The medical and dental coordinators, usually from the pre-clinical years, lead the discussions as patient files are carefully reviewed and students are assigned their patients. About eight medical patients are scheduled to be seen each evening; four of these usually fail to show up and an additional four simply walk in and ask to see the doctor. The occasional slow night when only three or four patients turn up at the Center is more than balanced by the nights when fifteen or sixteen patients present themselves and challenge the skills and efficiency of the student volunteers.

Each team has developed a substantial load of patients whom they see regularly and every attempt is made to ensure that continuity of care is maintained and that patients do not end up being seen by two or three teams at the same time. Of course, a patient who becomes acutely ill on Wednesday does not have to wait until the following Monday to be seen by the students who have been taking care of him in the past. Continuity of care is often a new experience for the patient who has previously received rather episodic medical attention in the outpatient and emergency departments of the downtown hospitals. Student-patient relationships may develop over the course of as many as three full years: for example, while working in the laboratory a first year medical student may encounter a patient whom he will meet repeatedly during his second year as a coordinator and in his third year role as a clinician. The opportunity for students to develop longterm relationships with patients is something that is both sadly lacking in the traditional health science curriculum and an attractive feature of the SHOUT program.

A student nurse is usually the first to see a medical patient presenting himself at the Center. She develops the initial rapport with the patient, records preliminary information pertaining to the patient's complaint and, depending on the situation, takes a pulse and blood pressure, cleans a wound, or even does a little supportive psychotherapy. The nurse is encouraged to do as complete a work-up as she can before presenting the patient to one or the two third year medical students. Often the nursing student will accompany the patient to one of the four examining rooms and assist the medical student in completing the history and conducting the physical

examination. This arrangement tends to make the patient feel more comfortable and allows for mutual support between the students. Together the students decide what should be done for the patient and then the medical supervisor is called in to check the students' findings and comment on their proposals for therapy. A consultation with a student pharmacist may help to answer any questions pertaining to drug dosages, contraindications and side effects. A group decision is then made, often after vigorous debate, and a plan for treatment and follow-up is implemented. The medical student writes the appropriate prescription and after it has been countersigned by the physician the pharmacist sees the proper drugs are dispensed and the patient adequately instructed in their use. (The Center's pharmacy stocks a wide variety of drugs which SHOUT provides free of charge to all patients.)

The format of patient care varies in response to patient needs. For example, an elderly woman who comes in to have a boil lanced will not be seen by the social worker. Similarly, the teenager whose mother has sent him to the Center to find out why he is having trouble at school is unlikely to encounter the pharmacy student in the course of his visit.

The student volunteers learn to work closely together in providing care for their patients. In doing this they acquire new skills and knowledge and come to recognize the skills and insights which are unique to members of the other health science professions and to appreciate the special contributions which each can make to the care of the patient.

A major thrust of the SHOUT health care program relates to preventive medicine. Student research[1] has demonstrated that only 58 percent of area residents have a family doctor. Documentation of the extensive use being made of hospital emergency departments by people without a regular family physician has indicated that many residents of Alexandra Park have a "crisis approach" to health care.[2] It is not surprising then that SHOUT has tried to encourage patients in preventive health practices. Check-ups (Complete General Assessments), well-woman and well-baby visits, vaccinations and allergy injections make up just over 15 percent of patient visits to the Center.

A large percentage of the 4500 people who live in Alexandra Park are children. Many of these youngsters present themselves with a variety of minor pediatric emergencies: cuts and bruises and even the occasional one who has been hit by a car. Most of the children's complaints are a little less dramatic than traffic accidents (we had two during the past summer) and take the form of rashes, colds and sore tummies. In most cases the children make delightful patients. However, those who are especially shy or of low intelligence present special challenges to student volunteers. Often several meetings with such a child are required before any lasting rapport can be established.

Many of the 350 residents of the Senior Citizens' building on Augusta Avenue present themselves at the Center with health problems that are chronic in nature. Arthritic, respiratory and cardiovascular diseases are common in this patient group. These patients need to be followed regularly and provide the students with an opportunity to participate in the longterm management of diseases which he is sure to encounter upon entering practice. While it is easy to read about the management of congestive heart failure in any textbook of medicine, participation in the actual management of such a case over the course of several months provides an opportunity to truly consolidate one's knowledge of the disease, its management and its complications.

Psychological complaints are common at the center as are physical complaints which have a significant psychosocial dimension. Patients often present themselves with minor symptoms which would not ordinarily require medical attention and upon having these symptoms dealt with begin to reveal something of the psychological or social problems which are troubling them. In many cases simple supportive psychotherapy is indicated while in others the complexity of the economic, social and psychological distress is beyond the student's ability to help. In this latter case the patient and his family may be referred to one of the social service agencies working in the area or to a consultant in psychiatry. The students learn to recognize psychological components in patient complaints and to deal with their own feelings about people whose social and psychological lives are different from their own. Occasionally relationships develop between students and patients that result in a good deal of benefit to both.

Dental facilities at the Center include five operating units, an x-ray unit and chair, and a special chair for prophylactic treatment and dental hygiene instruction. Senior dental students act as operators while pre-clinical students provide support as dental asistants. A faculty supervisor ensures that the students' work is satisfactory and is available to help the operators with any problems which they might encounter.

The dental health of the area residents has been well documented both by survey research[3] and by review of patient files. Suffice it to say that the dental health of this population is very poor and that the overwhelming demand for the dental services provided at the Center (all of which are free of charge to the patient) has established beyond question the importance of providing these services for the community.

The three senior dental students who work at the Center each evening are able to treat about eight scheduled patients between them. Sufficient time is left to see the two or three 'emergency' cases which turn up with astounding regularity.

When all the patients have been seen, and sometimes this is as late as 10:30, the students and their supervisors

sit down together in the Center's reception room and the 'post-clinic meeting' begins. These meetings are designed to provide a forum for student discussion of important medical, social and psychological factors relating to patients who have been seen that evening. The evening's activities are reviewed and students are provided with an opportunity to assess their own performance and that of other team members, supervisors included. The students are often openly critical of one another's behaviour both with respect to patients and to fellow members of their team. The student-nurses seem particularly adept at dressing down senior medical students who they feel have been insensitive to the feelings and needs of their patients. Additional topics of discussion range far and wide; from mechanisms of drug interactions to considerations of innovations in health care delivery.

The post-clinic meetings are an invaluable opportunity for students to pick up new technical information and to acquire new insights which may improve the quality of their relationships with patients and with other health care personnel. To some extent the post-clinic meetings reflect the early days of SHOUT when informal seminar discussions were the major focus of student activity.

Unfortunately, the SHOUT evening program does not always work out as well as has been described above. Pre-clinic meetings do not always take place. The physical separation of the medical and dental clinics is allowed to result in a lack of contact between the two. Ego-defense barriers develop between students from different professional faculties and prevent the development of personal and openly critical relationships between them. Post-clinic meetings are occasionally cut short or forgotten due either to the lateness of the hour or to the indifference of the students.

In spite of its shortcomings the SHOUT evening volunteer program provides an opportunity for nearly two hundred students to participate in an interdisciplinary team approach to the provision of primary health care services for a most interesting and challenging patient population.

## THE COMMUNITY HEALTH CENTER MODEL

A significant aspect of SHOUT's activities has been the development of a demonstration model for the delivery of primary health care services. In many respects the Alexandra Park Community and Health Center demonstrates the basic characteristics of a 'community health center' which were listed above.

1. The Center focuses on the needs of the underprivileged. The patient catchment area has 4,500 residents whose mean yearly family income has been documented as $3,550.[4] Almost half of the families in the area do not have a regular family physician (there are none practising in the community) and many rely on hospital outpatient and emergency departments for their primary health care. In a recent survey[5] which involved conducting dental examinations on a randomly selected sample of 144 adult residents of Alexandra Park, over half of the sample was found to be in need of immediate dental treatment and another 30 percent were found to be in need of dental treatment of a non-emergency nature. The cost of dental services is so high relative to incomes that most residents (90%) are unable to visit a dentist regularly (once per year).

2. The centrally located SHOUT clinic provides a full range of general practice medical services as well as basic preventive and restorative dental services. As well as being open in the evening the Center provides medical services on six half-days per week and dental services on four full days each week. (The daytime program is outlined below.) A physician is 'on-call' at night and on weekends to provide emergency medical coverage for the community.

3. The atmosphere of the Center is generally one of great warmth and personal concern. The decor is colorful and patients are treated to coffee and cookies as they wait in the comfortably furnished reception room. While continuity of care is sacrificed somewhat in that there is a turnover of students each year the patients seem to develop a loyalty to the Center which goes beyond their relationships with particular students. A major role of the public health nurse is to ensure that referrals are arranged and that appropriate patient follow-up occurs. While it is difficult to assess the quality of care which the Center provides we trust that a combination of student diligence and professional supervision will ensure that it is exemplary.

4. The Center integrates its care with other sources of services by having rapid referral arrangements with a number of specialists; by having arrangments with nearby laboratories to have lab work done which cannot be done at the Center; and by having the public health nurse in almost daily contact with the city nurse for the area to ensure that no overlapping of services occurs and that no patient needs are left unattended.

5. The SHOUT clinic has been involved in the development of an inter-agency group which meets regularly to coordinate the provision of health and social services in the Alexandra Park Community. Several agencies have assigned a worker specifically to Alexandra Park and the resulting increase in face-to-face interaction between agency personnel has resulted in much closer coordination of services.

6. The Center currently employs three women from the community as medical and dental assistant trainees. This is in accord with the original conception of community health centers in that they were

to provide training opportunities in the health field for residents of their service area. When three women are trained sufficiently that they can compete successfully on the open job market, new women will be taken on as trainees and similarly prepared for jobs in the health field.

Consumer participation in policy and decision making has been developing rather slowly at the SHOUT Center. For the past two years three members of the community have been voting members of the SHOUT Steering Council (executive). These people have taken an active role in the Center's activities but they and the students are generally dissatisfied with the extent of consumer participation to date. The fact that the Center was developed by students has been a factor in deterring community participation in its management and yet many members of the community seem indifferent to the concept. The students and citizens who are most active in the Center's operation are committed in principle to community control of the administration and management of the Center with students continuing their participation in the provision of health care. This is a different issue and its resolution will demand the good-will and dedication of students and citizens alike.

7. Federal support in the form of a National Health Grant ($25,000), private funding from the Physicians' Services Incorporated Foundation ($18,000 in the current fiscal year) and student contributions (approximately $15,000) combine to provide the bulk of SHOUT budget. Additional income derives from fee-for-service income from the medical program and from individual donations. Provincial and municipal involvement in funding, as well as greatly increased student support, will be critical in the future funding of the Center.

## FUTURE CONSIDERATIONS

In September of 1971 senior students in the Faculty of Dentistry began to come to the SHOUT Center during the day, four days each week, to provide additional dental care for the residents of Alexandra Park and to gain clinical experience in community dentistry. This daytime program is an official part of the fourth year dental curriculum and it distinctly characterizes the direction in which SHOUT is moving. SHOUT's goal is to have students from all of the health science faculties present at the Center during the daytime as part of an integrated curriculum. (To a limited extent this occurs even now since in addition to the students from the Faculty of Dentistry medical students are doing electives and nursing students are doing public health assignments at the Center.)

Before the SHOUT daytime program can be properly developed the students, staffs and administrations of all of the health science faculties of this university will have to reach agreement on the following general principles.

1. That if graduates in the health sciences are legitimately to be expected to work together in the provision of health care, then as undergraduates they should have a significant opportunity to learn to do so.

2. That the most appropriate student-student interactions will take place in the field and not in the lecture hall or seminar room. (Effectively, that students should learn to work together by working together.)

3. That the most appropriate time for this interdisciplinary interaction will vary from student to student and that, as a consequence of this, maximum flexibility must be a prominent feature of curriculum design.

4. That while some basic exposure to and participation in interdisciplinary interaction in a clinical setting is desirable for all students of the health sciences, the extent of this exposure and participation should be largely a function of individual student preference.

Having come to agreement on these basic principles it will remain to work out the mechanics of the program. This will require a tremendous amount of effort on the part of all concerned and given the present structure of the administration of health science education in this university it may prove a Herculean task. However, it can be done.

The SHOUT Center need not be the only focus of future programs in interdisciplinary education in the health sciences. There are a number of clinics within the system of university teaching hospitals where similar programs could take place. What is needed is broad agreement that programs in interdisciplinary education should be developed and the joint commitment of students, staff and administration to ensure that they do.

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*(continued on page 107)*

# *Tay-Sachs Disease*

*Stan Teitelbaum,* 7T2

## INTRODUCTION

Tay-Sachs Disease or infantile amaurotic familial idiocy, is a hereditary disease of lipid storage in which a specific ganglioside, $GM_2$, accumulates in the cytoplasm of the neurones of the brain. In recent years, attention has also been drawn to the fact that ganglioside is also increased in peripheral tissues, but to a much lesser extent, and Tay-Sachs Disease should thus be considered as a generalized disorder of ganglioside metabolism.[1] However, clinically, Tay-Sachs Disease manifests itself almost exclusively in the nervous system. Thus Tay-Sachs Disease is believed to be due to the occurrence of faulty metabolism of a lipid that is confined mainly to neuronal tissue.

## HISTORIC

In 1881, Warren Tay reported three cases of cherry-red macular degeneration with marked weakness of the trunk and limbs, in young infants of the same family. In 1898, Bernard Sachs named a heredodegenerative syndrome of arrested cerebral development with cherry-red macula occuring in Jewish children, Amaurotic Family Idiocy. Between 1939-1945, E. Klenk demonstrated that the brain in Amaurotic Family Idiocy or Tay-Sachs Disease (TSD) contains a marked absolute increase in the concentration of ganglioside and in 1958 Klenk sowed that the ganglioside which accumulated in TSD was $GM_2$. It was not until 1969 that Okada and O'Brien showed an actual enzyme deficiency in TSD.

## MODE OF INHERITANCE

TSD has been demonstrated to be due to an autosomal recessive gene, apparently with complete penetrance. When the disease was first recognized, it was believed to be found only in Jews, but verified cases in non-Jewish infants have been reported. It has also been established that TSD is more frequent among the Ashkenazi Jews than among other Jewish groups and the non-Jewish population. The Ashkenazi Jews are those Jews whose ancestors lived in central, eastern and western Europe and includes those who emigrated to North and South America, South Africa and Australia. In the United States the disease occurs once in approximately 6,000 Jewish births and once in approximately 500,000 non-Jewish births. On the basis of this birth incidence it is estimated that one of 30-40 Jewish persons and one of 380 non-Jewish persons is heterozygous for the TSD gene.[2]

## CLINICALLY

Infants affected with TSD usually show normal growth and development until approximately six months of age, when an insidious pattern of abnormal development becomes apparent. Early signs are listlessness or weakness, and difficulties in feeding, which at first may be attributed to other less serious causes. However these signs tend to progress to motor deterioration. An exaggerated extension response to sound, which has erroneously been called hyperacusis is one of the earliest clinical signs to appear. The production of a sudden sharp sound, not necessarily loud, will elicit a sudden extension of the upper extremities and a startled facial expression. The motor reaction resembles decerebrate posturing and myoclonus.[3] Inability to sit up, listlessness, or lack of awareness, inability to hold the head up and abnormal limb movements are other common initial diagnostic features. The main visual disturbance is blindness which progresses during the 2nd year of life and is usually complete by 2 years. This can be suspected clinically by fixed gaze, abnormal eye movements or visual inattentiveness. The fundus almost always shows a macular cherry-red spot. Epileptiform seizures or convulsions occur as the neurological symptoms progress and eventually the child reaches a completely vegetative state. Most affected infants survive for no more than 36-48 months, but with expert nursing care longer survivals have been reported.

## PATHOLOGY

Grossly, the brain may vary greatly in size depending on the age of death of the infant. In patients dying at a very early age, the brain tends to be firm and leathery in consistency and appears to be diffusely atrophic with moderate ventricular dilatation. Those dying later in the course of the disease tend to have enlarged brains due to a reactive proliferation of the glial cells and intraneuronal storage of ganglioside. The brain of these infants may be up to 50% greater in weight than normals. However the cerebellum usually fails to increase in size and weight.[3]

Histologically, there is a marked distortion of the cytoarchitecture without predilection for any single cortical layer. The ganglion cells are greatly distended and ballooned out, and most of the cells nuclei are displaced peripherally or are destroyed. The cytoplasm tends to be pale and spongy in appearance. Nissl bodies gradually decrease and eventually disappear leaving a halo of granular substance behind. The glial cells proliferate and hypertrophy and show the appearance of foam cells or fat granule cells. These changes in the glial cells appear to increase in severity the longer the patient survives, thus accounting for the megaloencephaly seen late in the disease. However, in the cerebellum there appears to be only a mild glial reaction. In the spinal cord the anterior horn cells are much more involved than the posterior horn cells. The neurones of the autonomic nervous system are also involved.

The axons are in various stages of disintegration and eventually decrease in number, especially in the cerebral cortex. The brain stem and optic radiation show relatively little reduction in axons. Demyelination may become quite extensive and can involve the entire white matter.

With the electron microscope, numerous round or oval membranous cytoplasmic bodies are found in the ganglion cell nuclei. These consist of concentric layers of dense material 0.5-2.0 microns in diameter, and are believed to represent a spontaneous aggregation of gangliosides which have accumulated because of the biochemical defect. It has not been conclusively determined whether these membranous cytoplasmic bodies are altered lysosomes or are completely unrelated to cellular organelles. Isolation and a chemical analysis of these membranous cytoplasmic bodies show them to contain 57% ganglioside, 22% cholesterol and 11% phospholipid, the other 10% being miscellaneous materials.[3]

The cherry-red macular spot is produced by storage in the retinal cells which is identical to the storage in the ganglion cells in the brain. The cherry-red spot consists of a gray to gray-yellow zone in the macular region in which the fovea is seen as a red spot. The grayish macula is believed to be due to oedema and swelling of the internuclear layers on either side of the fovea, or to swelling and necrosis of ganglion cells.[4] This results in the unmasking and framing of the underlying vascular choroid. Occasionally degeneration and demyelination of the optic nerve also occur.

## BIOCHEMICAL

The gangliosides are ceramide oligosaccharides substituted with one or more N-acetylneuraminic acid (NANA) residues. A ceramide (Fig. 1, c) consists of a fatty acid (Fig. 1, a) joined in amide linkage to sphingosine (Fig. 1, b), or one of its derivatives.

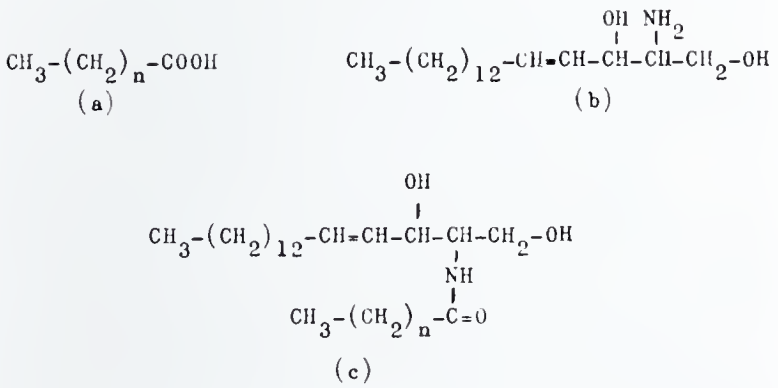
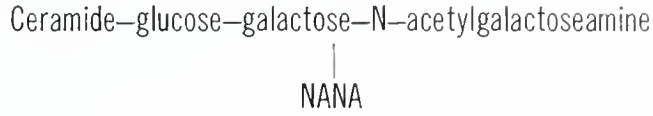



Figure 1. Structure of Ceramide (c) and its component parts (a, b).

Ceramide becomes a ganglioside by the addition of i) hexoses and or hexosamines to the C-1 of the ceramide and ii) NANA residues to a hexose residue or another NANA residue. The gangliosides are subdivided into those containing one NANA (GM), two NANA (GD), and three NANA (GT). They are further subdivided on the basis of their hexose constitution.

Little is known about the physiological role of the gangliosides. Because of the severe neurological disturbances resulting from inborn errors of ganglioside metabolism, it is believed that these compounds are essential to normal nerve physiology. It has been shown that gangliosides play a role in water and potassium ion distribution in brain tissue and that they have a protective action against certain viruses and bacterial toxins.[3]

In TSD there is an accumulation of the ganglioside $G_{M_2}$ in the brain. The structure of $G_{M_2}$ is as follows:




This differs from the preponderant monosialoganglioside $G_{M_1}$ in the brain in that a terminal molecule of galactose is missing. (Fig. 2.)

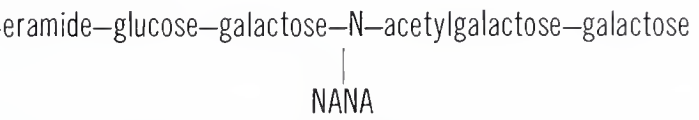



Figure 2. Structure of $G_{M_1}$. Compare with structure of TSD ganglioside ($G_{M_2}$) shown above.

The absence of this galactose molecule in $G_{M_2}$ led to the postulation of three possible enzyme defects in TSD. The first is a deficiency in a galactose tranferring enzyme necessary for the completion of normal $G_{M_1}$. (Fig. 3.)

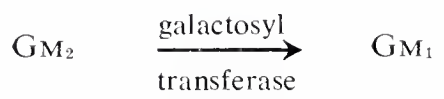



Figure 3. Site of one postulated enzyme block in TSD.

If this postulated enzyme block was the abnormality in TSD one would expect a decrease in $G_{M_1}$ in the brain of infants with TSD. However it has been shown that $G_{M_1}$ is present in normal amounts in the brains of TSD infants.[5]

The two alternate sites for an enzyme defect in TSD are both involved in the catabolism of $G_{M_2}$ (Fig. 4).

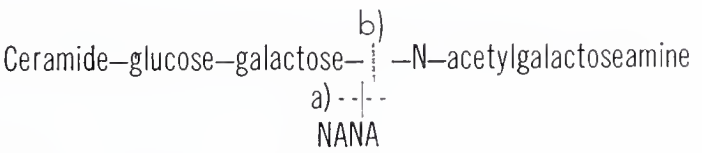



Figure 4. Structure of $G_{M_2}$ and sites of possible enzyme defects.

A deficiency of a NANA cleaving enzyme (Fig. 4a) is one such abnormality possible in TSD. Kolodny et al showed however, that there was no deficiency in a NANA cleaving enzyme in TSD.[6]

The second possible abnormality is a deficiency in a N-acetylgalactoseaminyl cleaving enzyme or hexosaminidase (Fig. 4b). It was shown however that cerebral tissues of patients with TSD have elevated hexominidase activity compared to normals. Okada and O'Brien and independently Stirling and Robinson showed, however, that in normal subjects there are two hexosaminidase components present in all tissues, hexosaminidase A and hexosamindiase B. Both compounds have acetylglucosaminidase and acetylgalactosaminidase activity, the former

being eight times greater than the latter. However, in tissues from infants with TSD, hexosaminidase A was found to be absent; the activity of hexosaminidase B was markedly increased in the cerebral cortex of patients with TSD, thus explaining the high levels of hexosaminidase activity found in the cerebral tissues of those with TSD. O'Brien and Okada also showed that hexosaminidase A is the major hexosaminidase in normal human venous blood and only traces of hexosaminidase B are present. However in TSD, hexosaminidase B is the only component found in the blood. Thus an enzyme deficiency was demonstrated in TSD.[7,8]. However, O'Brien and Okada failed to demonstrate that hexosaminidase A participates in the catabolism of $G_{M_2}$. This was accomplished by Kolodny in 1969. $G_{M_2}$ was prepared and labeled at the N-acetylgalactosaminyl moiety. Hexosaminidase was isolated from muscle preparations from normals and from infants with TSD. The hexosaminidase isolated from normals did catabolize $G_{M_2}$ at the N-acetylgalactosaminyl moiety. However, this activity was lacking in muscle preparations of hexosaminidase obtained from patients with TSD.[9] Thus in TSD a deficiency of an enzyme, hexosaminidase A necessary for the metabolism of $G_{M_2}$ has been demonstrated. Because of the deficiency in hexosaminidase A, $G_{M_2}$ accumulates in the brain of those with TSD.

## DIAGNOSIS & PREVENTION

Further work with hexosaminidase showed that hexosaminidase A and B have different thermal susceptibilities. Hexosaminidase A is labile to heating at 50°C. After four hours of heating at 50°C, 95% of the activity of A and less than 5% of the activity of B is inactivated. This is the basis for a serum assay for the detection of heterozygotes and homozygotes for the TSD gene. According to the method of O'Brien and Okada, serum from those to be tested is added to each of eight stoppered test-tubes. One tube is kept as a blank, three tubes are frozen immediately, two tubes are heated at 50°C for three hours and two tubes are heated at 50°C for four hours.

Then under optimum conditions (pH 4.4, 37°C), a synthetic substrate (4-methyllumbelliferyl-N-acetyl-$\beta$-D-glucosaminide) is added to all test tubes except the blank. After one hour the reaction is stopped, substrate added to the blank, and the extent of substrate cleavage is determined by a fluorescence method. The activity of the enzyme in each tube is determined in nanomoles of substrate cleaved/ml of serum. The activity of hexosaminidase A is determined as the activity of the enzyme which is inactivated by heating.

By this method, O'Brien showed that parents of affected children and children with TSD had levels of total serum hexosaminidase activity that were no different than in normal controls.[10] However, the percentage of hexosaminidase activity due to hexosaminidase A was markedly different in the three groups. (Table 1)

Table 1. Total Hexosaminidase Activity and Hexosaminidase A Activity[9].

| Group | Mean Total Hexosaminidase (Nmoles/ml/hr | Hexosaminidase A (% of total) | (range) |
|---|---|---|---|
| Controls | 575 ± 114 | 57.3 ± 5.4 | 49–68 |
| Parents | 450 ± 96 | 37.5 ± 6.4 | 26–45 |
| TSD | 539 ± 301 | 1.7 ± 1.1 | 0–4 |

Since the value of hexosaminidase A activity in obligate heterozygotes i.e. the parents of children with TSD is only two thirds that of normals, O'Brien et al feel that this is a useful screening test for heterozygotes in the susceptible Jewish population. However this method cannot be used in those with diabetes mellitus, severe illnesses and in early infancy and most importantly in pregnancy. This test is also diagnostic of the homozygote who by definition must have TSD. A modification of this test has been developed for use in pregnancy. By assaying hexosaminidase A activity in the white blood cells, instead of serum of pregnant females, heterozygotes can be detected.

What can be done in the pregnant female where spouse and she are both known to be heterozygotes? In a study by Schneck *et al*[1], amniocentesis was performed during the second trimester on a mother who had already given birth to one child with TSD. The level of hexosaminidase A activity of the uncultured cells and fluid was determined. Since the activity of hexosaminidase A was found to be low, the pregnancy was terminated. The aborted fetal tissue showed a concentration of ganglioside in the brain four and one half times the concentration found in normal similar age abortus. No activity of hexosaminidase A could be detected in the tissues of the abortus. This study suggests that amniocentesis is an important and perhaps the definitive aid in the prenatal diagnosis of TSD. At a recent meeting of sphingolipid chemists in New York in 1971, it was reported that at least 60 pregnancies had been monitored by aminocentesis, and over 20 pregnancies were terminated because of the prenatal diagnosis of TSD[12].

## SUMMARY

TSD, a fatal inborn error of ganglioside metabolism, due to the absence of hexosaminidase A activity, is a disease which can be eradicated if the high risk Ashkenazi Jewish population is screened for heterozygotes and appropriate genetic counselling given to those found to be carriers of the TSD gene. At present, a carrier screening programme is being begun in the Jewish population of Toronto that will hopefully reach all married couples in the child-bearing age group (18-43). Hopefully this mass screening will prevent the occurrence of this disease in the Toronto area.

*ACKNOWLEDGEMENTS*

*Many thanks to Dr. J. A. Lowden for his valuable help in preparing the manuscript.*

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# *A Patients' Pamphlet For Malignant Hyperthermia*

*John Frank, B.Sc.,* 7T4

The following is a recent summary of known facts about a rare hereditary disorder, malignant hyperthemia. However, this summary differs from a scholarly abstract or literature review; it is written for the families of the patients who are malignant hyperthermic reactors. Today medicine is defining and treating more hereditary disorders than ever before. In these clinical situations, the physician must be able to fully explain the significance of the disorder to the patient and his family, in such a way as to equip them to adjust to the presence of the new factor in their lives. The following is an example of the kind of "patients' pamphlet" that can often greatly assist the clinician in such situations. If written in a style and a vocabulary that make the concepts clear to the patient, whether he has a public school education or a college degree, the "patients' pamphlet" can save the clinician much valuable time and ensure that the patient's family does in fact reach a full understanding of the problem. The following is offered in the hope that others might be hereby encouraged to do similar translations from medicalese into everyday language for the use of patients with other chronic medical problems, especially hereditary ones. It is also hoped that by reading this, a few more physicians might become familiar with the very serious condition known as malignant hyperthermia.

*What is malignant hyperthermia?*

Malignant hyperthermia, or MH as it is often called, is a rare reaction to some drugs which occurs only in some persons. These persons, which are MH-reactors, cannot be given either of two kinds of drugs that are normally used to prepare a patient for surgery. These drugs are the potent inhalational anaesthetic agents and the muscle relaxants. If these "triggering drugs" are given to a MH-reactor a very serious reaction may take place due to an enormous acceleration of muscle metabolism. To date, of the patients who have undergone such an episode about two thirds have died, despite all efforts by skilled medical personnel to save them.

*What is an MH reaction like?*

The most obvious symptom of such a reaction is a very high fever. It is this fever which gives the condition its name — "hyperthermia". The word "malignant" as used here does *not* indicate any connection with cancer — it just means that the reaction is very serious. About three quarters of reacting individuals develop a profound muscle stiffness or rigidity. The remaining quarter do not. Their muscles stay in the normal relaxed state. On the basis of whether or not muscle rigidity is present, MH is considered to occur in two forms: the rigid and the non-rigid varieties.

*How rare is MH?*

Whether or not a person is a MH-reactor depends on heredity. Therefore, MH is common within families in whom MH has occurred. If such a family is large and most of its members live within a small area, the condition will be common in that area. But in the general population, MH is believed to affect about one in every fifteen thousand people.

*Who is affected by MH? Is there a cure?*

Persons of any age and either sex may be MH-reactors. Once it is established that a person is a MH-reactor, he or she will always have to avoid the two categories of drugs mentioned above. Prevention of acute episodes is the best cure. No one can be cured of the tendency to react to these drugs, should they be given.

*How does one get MH?*

One cannot "catch" MH from another person. Those who are MH-reactors are born as such and, usually (although not always) at least one of the parents is also an MH-reactor. Thus MH is passed from one person to another only in the sense that an affected person can give it to his or her child.

*How is MH inherited?*

In a family where either the mother or the father is a MH-reactor, one may say that each child has a fifty per cent chance of being born as an MH-reactor. This is like saying that each child has a fifty per cent chance of being born a boy. Although these statements are true, they can never tell us what the situation is going to be for any particular birth. We don't know ahead of time whether the next child is going to be a girl or a boy. In the same way, in a family where one parent is an MH-reactor, there is no way of predicting whether or not the next child born in that family will be an MH-reactor.

*What things are predictable about the inheritance of MH?*

The most important fact about MH inheritance, already pointed out above, is that if one is born as a MH-reactor, one's children will have a fifty per cent chance of being born a MH-reactor. Of course the exact proportion of affected and un-affected children that each second generation family will have is as unpredictable as was the proportion in the family before it. But the important fact to remember is that for every child in whom the condition appears, there is the chance that some of his or her children will have it too. What about those children of an MH-reactor family who are not affected? Usually, all of their children, grandchildren, great-grandchildren and so on will also not be affected. Thus, in a family tree that shows MH, some branches are likely not to have the condition. It is quite possible that just by chance, none of the children of an MH parent will be MH-reactors. This can happen as easily as a family can have all boys.

*Are there exceptions to the rules of inheritance?*

Yes. First of all, if the pattern outlined above always held true, it would mean that no one could ever be born as a MH-reactor unless at least one of his or her parents were also one. There are rare exceptions to this. In some

families certain individuals do not seem to be affected with the condition and yet their children are. We call this "generation skipping". In such cases, usually one of the grandparents is or was a MH-reactor. This would mean that the alteration which causes MH was present in the grandparents and grandchildren, but skipped the middle generation for some reason. At the present time we do not have an explanation for this phenomenon. Further research may provide the answer.

*What specific drugs cannot be given to a MH-reactor?*

Almost all potent inhalational anaesthetic agents cannot be given to a MH-reactor. These are the gases and vapours inhaled by the patient to "put him to sleep" and to keep him asleep during surgery. Nitrous oxide or "laughing gas" is a clear exception: it being a very weak anaesthetic it is not dangerous to MH patients. Among those anaesthetic gases and vapours that are dangerous to MH-reactors are: ether, Trilene (trichloroethylene), Fluothane (halothane), Penthrane (methoxyflurane) and cyclopropane, etc. None of the muscle relaxants, which are normally used to relax the muscles and so make the sugeons' work easier, can be given. They include Anectine (succinylcholine), Syncurine (decamethonium), Flaxedil (gallamine) and curare.

*How is surgery performed on a MH-reactor?*

Because there are now alternative drugs that do not cause MH in MH-reactors, modern hospitals can perform any operation that an affected patient may require. MH-reactors need never go without surgical treatment because of their condition.

Among these alternative drugs are the local anaesthetics, which are used to "freeze" one part of the body just as a dentist "freezes" the jaw so no pain can be felt. They may be given at the site of surgery as a regional block, or as a "spinal" or "epidural". Both of these latter two techniques eliminate pain from the entire lower half of the body. Other good drugs are capable of "putting the patient to sleep" much as the potent inhalational anaesthetic agents do. Among these are the barbiturates such as Sodium Pentothal, the narcotics, such as Demerol (meperidine) and the new neuroleptanalgesics, such as Innovar. Thus for any surgical situation that a MH-reactor may be in there is some combination of good alternative drugs that will do the job.

*Are there any real problems associated with being a MH-reactor?*

Most MH-reactors lead a completely normal life. They need only inform their doctors of this condition so that any surgery can be planned accordingly. And if in an emergency they are brought to a strange hospital and are for some reason unable to communicate, an appropriately inscribed Medic Alert bracelet will warn physicians of their condition.

*The real problem with MH is to find out which people are reactors before they undergo a regular preparation for surgery.*

A few very severely affected individuals have learned by experience that they should avoid strenuous exercise such as weight-lifting, football, and hockey. In these persons such exercise may by itself cause sufficient muscle damage to precipitate an acute MH reaction.

*How is a MH-reactor detected?*

Obviously those persons who have had an acute MH episode and are still alive are diagnosed as being MH-reactors. However, there are many reactors who have not experienced such a reaction. These fall into two categories. There are those who have been exposed to some of the triggering drugs and who have not reacted. And then there are those who have never been exposed to any of the triggering drugs. The latter group we can draw no conclusions about. One might think that the former group, on the other hand, might not be susceptible to MH. However, it happens that there are numerous records of MH-reactors who did not react to triggering drugs on the first or even second exposure, but who developed serious reactions the third time the drugs were given. Others have proved to be malignant hyperthermic only on the fourth exposure to such drugs, and so on. Given these facts (which researchers are now trying to explain), we can see that almost any number of normal exposures to the triggering drugs is no proof that the next exposure won't provoke a serious MH reaction.

Therefore, in order to get around the difficulties of trying to decide who is a MH-reactor from just reading patients' medical histories, blood tests are being devised to tell safely and easily whether or not a person is a MH-reactor.

*What is the blood test for MH-reactors?*

The test to detect MH-reactors is called the serum CPK (creatine phosphokinase) test. It requires only a small sample of blood which can be easily taken right in one's home or in the doctor's office. The blood is processed immediately to make it into serum. This serum is then stored in a freezer until a measurement can be made of the amount of CPK in it. CPK is a chemical belonging to the group known as enzymes. CPK normally occurs in the serum in very small amounts. Most of it is present inside the muscles of the body. In most MH-reactors, however, some CPK has escaped into the serum in larger amounts than normal, so we say the level of CPK in the serum is "elevated". This in itself does not seem to affect the person adversely, but it is an indicator which shows that MH could occur. Therefore, persons with elevated serum CPK levels must avoid general anaesthetics and muscle relaxants. There are other conditions, not related to MH, such as heart attack and muscular dystrophy, which can also cause elevated serum CPK levels. But we are talking here of elevated serum CPK that is not due to any of these other conditions, which are by and large easily recognized.

*How is the test interpreted?*

The results are given as the number of units of CPK in the serum. At the Toronto General Hospital, where

all of the University of Toronto samples are processed, normal values range from 5 units up to 40 units for women and children and from 5 units up to 50 units for adult men. The difference here is due to the larger amount of muscle in the adult male. Levels of serum CPK above 80 units for men or 60 units for women and children are considered genuinely elevated levels. This leaves levels between 60 and 80 for men and between 40 and 60 units for women and children. Such levels are termed "borderline" and are difficult to interpret. Results that are borderline necessitate a repeat testing. Further results definitely above or below the borderline zone then make it possible to say whether a person is a MH-reactor. (NOTE: This guide for interpreting results is not valid for results produced in other hospitals or other laboratories. Every testing place has its own range of normal values, since every testing place has a slightly different way of doing the test.)

*Is the test impossible to interpret in some cases?*

There are people for whom the test will not give clear cut results. For example, some people consistently show borderline test results time after time. Then there are people in whom the measured serum CPK level varies so much from time to time that some test results for them will be elevated, while others will be normal.

Interpretation of such ambiguous test results must always be on the safe side. When in doubt, we consider the person to be a MH-reactor. This way, whether we are right or wrong, no harm comes to the person in question. By avoiding the two categories of triggering drugs already mentioned, the patient plays it safe at no cost to his health. For, as outlined above, there are plenty of alternative ways of preparing him for surgery.

This "play it safe" policy must also be followed whenever children under three years of age are suspected of being MH-reactors, for serum CPK tests are meaningless in this age group.

*Are these tests foolproof when the interpretation is not in doubt?*

In families with only the rigid form of MH, a consistently normal CPK level is presently felt to be proof that an individual is not a MH-reactor. That is, in such a family, the CPK is always elevated in those persons who have the disease. This means that these tests are reliable in about three quarters of the families in which the disease has been discovered so far.

However, in any family wherein a non-rigid MH reaction has occurred, the serum CPK test is not totally reliable. The test may detect some MH-reactors but not all of them. For it now appears that some persons who have the non-rigid form of MH have normal serum CPK levels. In such families, these tests should nevertheless be done since at least some MH-reactors may be found. An attempt is presently being made to find new tests that will detect persons susceptible to the non-rigid form of MH in a more reliable way. Until then, all individuals in families with the non-rigid form of the condition should be treated as if they were MH-reactors and any surgery planned accordingly.

*What is being done to prevent further illnesses and deaths from MH reactions?*

Because potent inhalational anaesthetic agents and muscle relaxants are very useful and good drugs for all but one fifteen-thousandth of the general population, these drugs will continue to be used in surgery. Because most MH-reactors have no special problems unless they need surgery and because the CPK test is expensive, screening of the general public for MH is not the most practical way to prevent MH reactions. At the present time, all prospective surgery patients should be screened by doing CPK blood tests when MH reactors are in the family. Any patients shown to possibly have malignant hyperthermia would then be given the alternative pre-operative drugs. Since MH is still a newly discovered disease one cannot yet rely on all hospitals to automatically perform the CPK tests. If you are a member of an affected family, you are therefore advised to request from your physician that the CPK test be done when a relative has to undergo surgery. There is one other good way to find MH-reactors and warn them. This is to simply follow up the family trees of all reported cases of MH reactions. Blood tests are then done on all the living relatives of the person who has had the reaction. (Generally, only "blood" relatives are tested — there is seldom any reason to test those who have married into the family.) Many, many MH-reactors are discovered in this way and thus protected by a Medic Alert bracelet before they are planning any surgery.

In addition, research into MH goes on.

*What kinds of MH research are presently being carried out?*

One of the main areas being investigated today is the MH reaction itself — how it works and hopefully from this, how to control it and bring the patient out of it alive. As long as there remains even one undiscovered MH case, and many still exist today, this is an important field.

Another area of investigation surrounds the question of better tests to detect MH-reactors, ones that will work for all forms of the disease. At the present time, there is reason to believe that much progress will soon be made in this area.

Finally, research is being conducted into the cause of MH — the defect in muscle cell which causes it to respond abnormally to potent anaesthetic agents and skeletal muscle relaxants.

From these three angles then, research is trying to reduce both the incidence and severity of acute MH episodes. Hopefully, within a few years such reactions will have become a thing of the past.

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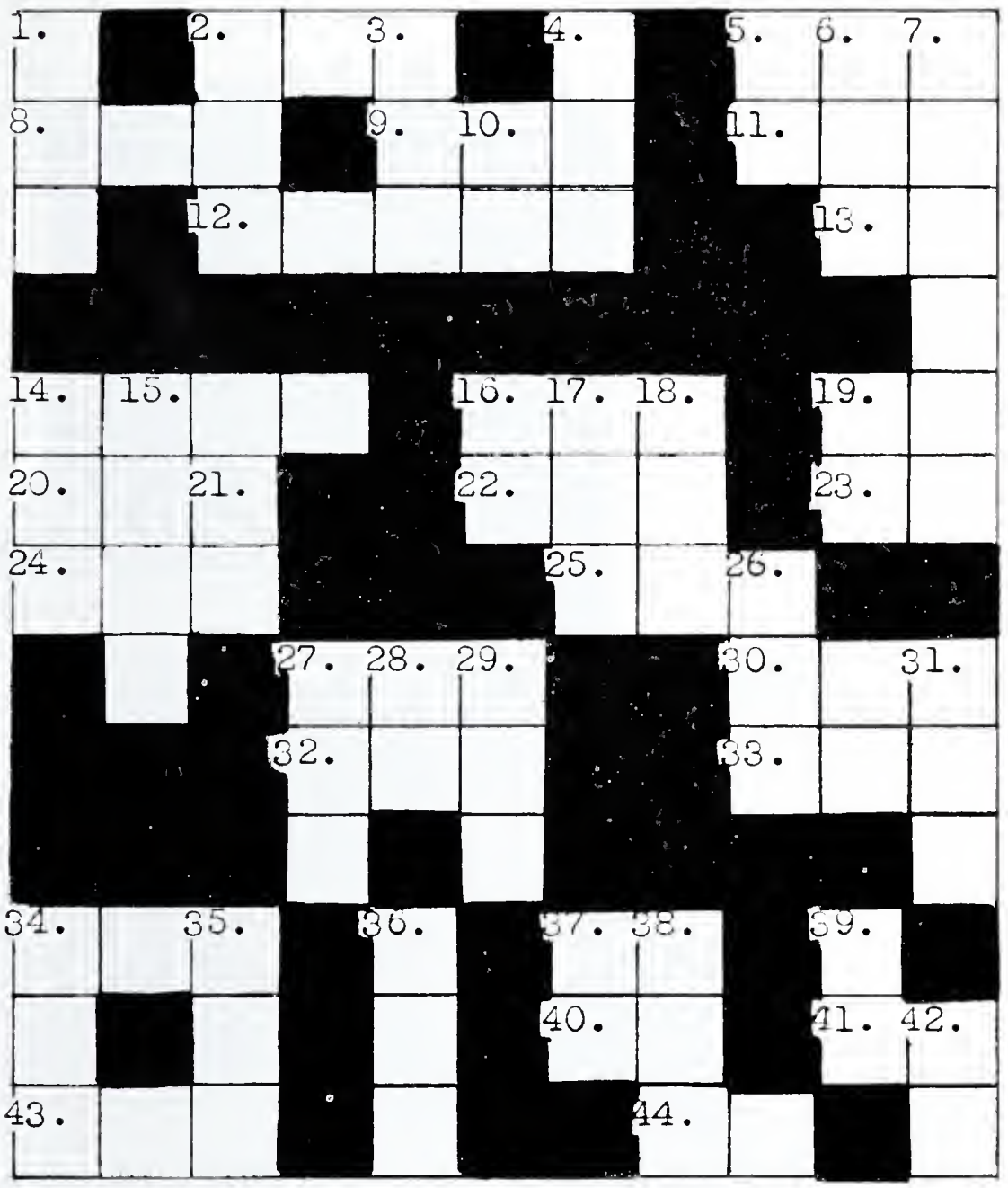
# *Crossword Of Medical Abbreviations*

*Frank W. Rosenberg, 7T2*



**ACROSS:**

2. dental surgeon
5. hormone like ACTH
8. azotemic titer
9. monitoring unit
11. dependent edema
12. neonatal score
13. arterial tension
14. hepatocellular enzyme
16. supraventricular arrhythmia
19. Crohn's disease
20. common parturient presentation
22. sequela of tertiary lues
23. head and neck (abbrev.)
24. preoperative examination
25. coronary unit
27. operation for deviated septum
30. thyrotropin
32. twice daily
33. type of purpura
34. P, QRS, T waves
37. degenerative joint disease
40. consumption
41. x-ray taken from front
43. treatment for psoriasis
44. stenotic mitral valve opens

**DOWN:**

1. serum iodine titer
2. nucleic acid
3. label (Lat.)
4. type of prostatectomy
5. demyelinating disease
6. dyspnea
7. incomplete antigen
10. mitotic lesion
14. malar rash plus arthritis
15. monoarticular arthritis
17. analgesic compound
18. habit spasm
19. erythroblastosis fetalis
21. ethanolics association
26. G-U infection
27. PUO plus heart murmur
28. coronary
29. hyaline membrane disease
31. history of present illness
34. shock out of depression
35. measurement of renal filtration
36. brain wave tracing
37. activities of daily living
38. blood group
39. seropositive arthritis
42. vitamin B-12 deficiency anemia

SHOUT (continued from page 99)

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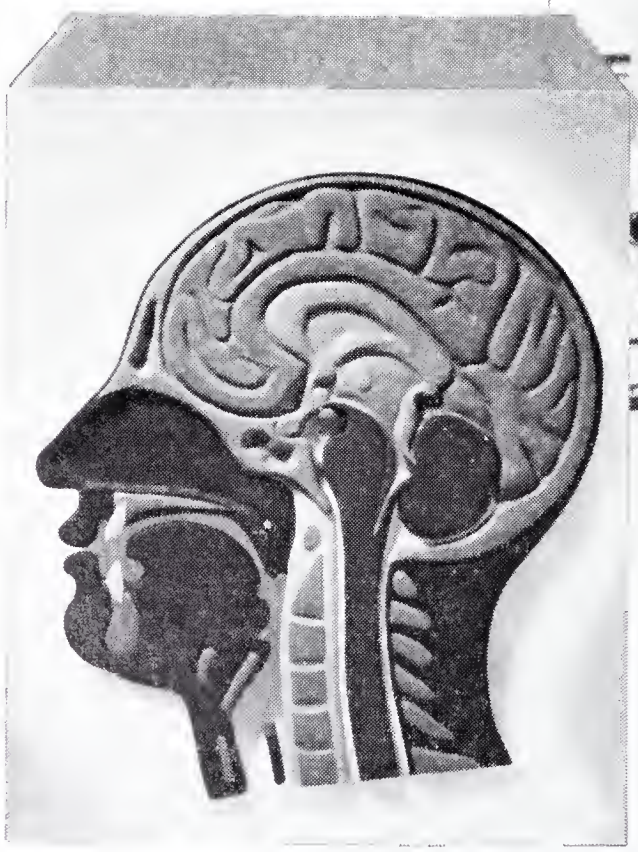

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